科技部補助專題研究計畫成果報告
期末報告

離散事件模擬法與慢性肝病進程之預測(I)

計 畫 類 別 ： 個別型計畫
計 畫 編 號 ： MOST 103-2221-E-004-003-
執 行 期 間 ： 103年08月01日至104年09月30日
執 行 單 位 ： 國立政治大學應用數學學系

計 畫 主 持 人： 陸行

計畫參與人員： 大專生-兼任助理人員：林家民
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大專生-兼任助理人員：周俊川

報 告 附 件 ： 移地研究心得報告
出席國際會議研究心得報告及發表論文

處 理 方 式 ：
1.公開資訊：本計畫涉及專利或其他智慧財產權，1年後可公開查詢
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中 華 民 國 104 年 12 月 28 日

中 文 摘 要 ： 慢性B型肝炎病毒(HBV)感染是一個動態的過程，具有初期之複製階段和活
躍的肝炎病毒感染史。HBV能導致長期的感染並且引起嚴重的臨床和診療問題，
影響全世界至少4億的人口。然而，目前某些難解的問題仍無法以現存的臨床資
料處理。這些問題包括預測B型肝炎的自然進程和有關它的治療成本效益。雖然
世界上已有很多國家在考慮一些決策模型中使用不同的診療策略來比較和分析
其成本效益，但是離散事件模擬法(Discrete Event Simulation)可以設定不同的研究
標的，是一種了解HBV情境過程靈活又強有效的分析工具。本計畫主要的目的是
以台灣醫學專家的臨床資料和數學決策模型，運用資料庫資源，建立決策支援系
統模型，以協助醫生觀察和了解不同醫療決策所可能造成的影響。

中 文 關 鍵 詞 ： 電腦模擬 肝炎病毒感染流程 數學決策模型

英 文 摘 要 ： Chronic hepatitis B virus (HBV) infection is a dynamic process with an early
replication phase and active liver disease. HBV can result in long-term infection
causing a serious clinical problem, affecting 400 million individuals worldwide.
Several unresolved issues are difficult to address using currently available clinical
data. These include prognosis of hepatitis B with its natural history and the relative
cost-effectiveness of the management procedures. Although some decision models
with different strategies are used in many countries across the world to consider the
cost-effectiveness of alternative healthcare interventions, Discrete Event Simulation
(DES) presents a flexible and powerful analysis tool for respective purposes in HBV
studies. A model of decision support system is developed for providing alternative
suggestions of treatments based on simulation outputs for prognosis for progression of
HBV infection.

英 文 關 鍵 詞 ： Computer simulation, HBV infection, Mathematical decision models

科技部補助專題研究計畫成果報告

（□期中進度報告/ ■ 期末報告）

離散事件模擬法與慢性肝病進程之預測(I)

（計畫名稱）

計畫類別：■個別型計畫　□整合型計畫
計畫編號：MOST 103-2221-E-004 -003 -
執行期間： 103 年 8 月 1 日至 104 年 9 月 30 日

執行機構及系所：

計畫主持人：陸行
共同主持人：
計畫參與人員：周俊川、詹志敏、林家民、杜靖凱

本計畫除繳交成果報告外，另含下列出國報告，共 _2__ 份：
■ 執行國際合作與移地研究心得報告
■ 出席國際學術會議心得報告

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中　華　民　國　104　年　9　月　28　日

附件二

科技部補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現（簡要敘述成果是否有嚴重損及公共利益之發現）或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估
   - □ ■ 達成目標
   - □ 未達成目標（請說明，以 100 字為限）
     - □ 實驗失敗
     - □ 因故實驗中斷
     - □ 其他原因

   說明：

   在計畫第一年的預期目標下，我們達到建立離散事件模擬法與慢性肝病進程的計算模式，完成論文如後頁所載。這個模式可以幫助爾後開發肝病預防與治療的決策支援系統，有助於進行藥物經濟之成本效益分析。

2. 研究成果在學術期刊發表或申請專利等情形：

   論文：□已發表 □■未發表之文稿 □撰寫中 □無

   專利：□已獲得 □申請中 □無

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   其他：（以 100 字為限）

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性），如已有嚴重損及公共利益之發現，請簡述可能損及之相關程度（以 500 字為限）

   論文的學術成就在於推導 time-nonhomogeneous markov chain 計算的基本性質，以不同的機率條件驗證其收斂性和以不同模式(計算軟體)驗證其可行性。其應用在建立可計算的肝病病程的數學模型和電腦模擬程式。本計畫提供計算肝病病程風險預測的模式，其計算模式可運用相關的研究和支援健保經濟政策擬定。

HBV Infection Prognosis Prolonged Simulation Models

ABSTRACT

Objectives: Chronic hepatitis B virus (HBV) infection is a dynamic process with an early replication phase and active liver disease. HBV can result in long-term infection causing a serious clinical problem, affecting 350-370 million individuals worldwide. Several unresolved issues are difficult to address using currently available clinical data. These include prognosis of hepatitis B with its natural history and the relative cost-effectiveness of the management procedures. Markov models and decision trees are commonly used in disease progression simulation. However, these methods cannot reflect the clinical appearance more flexibly and alternatively. Therefore, this requirement develops a discrete-event computer simulation model for the analysis of HBV disease progression. Discrete Event Simulation (DES) presents a flexible and powerful analysis tool for respective purposes in HBV studies. In this paper, we developed a DES model based on the natural course of HBV infection. The celebrated Gompertz function and the life table are applied the developed model. The model is effective by resembling individuals or cohorts of hypothetical patients while tracking disease progression and survival.

Methods: We consider that the disease progression is originally described by a Markov model, and propose a new method to approximate the HBV progression with clinical data. Instead of the additive assumption, this resulting model is established based on conditional probabilities and a life table.

Results: For a patient at age 25, the expected remaining life expectancy, and the maximal life year for him or she is 36.31 years and 80 years respectively. This patient has 16.37% probability of death/transplantation within 20 years because of HBV infection or population mortality.

Conclusion: Numerical results show that the proposed model can be applied to obtain a more realistic life expectancy, the survival probabilities at various initial ages, and mortalities from various initial symptoms to death. Meanwhile, its applications to derive the probabilities for patients' first experiencing critical medical status during a specified duration and its generalization to include multiple transition related factors are discussed.

Keywords: Markov chain, disease progression, life table, first passage time, survival probability.

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1. Introduction

Simulation in healthcare as an academic subject has been widely explored and well doucmented. During the past decades, simulation modeling in healthcare has been referred to wide range of

applications from health risk assesssment, cost-benefit analysis and policy evaluation of medical treatment, diesase menagement, planning of healthcare services, training and healthcare decision support system, etc. [15], Computer simulation is a technique of informatics which allows stake holder to conduct experiments with model and ideally provides a communication platform in healthcare for administratiors and clinicians to to find better solutions for patients or tax payers.

Chronic hepatitis B virus (HBV) infection is a dynamic process with an early replication phase and active liver disease. HBV can result in long-term infection causing a serious clinical problem, affecting 350-370 million individuals worldwide. Disease progression modeling is generally recognized as a practical framework in considering related medical applications. Chronic hepatitis B inflicts an almost incredulous toll on the planet, affecting greater than 400 million people [11]. In Taiwan, chronic hepatitis B virus (HBV) infection and its potential adverse sequel are major causes of morbidity, mortality and medical expenditure. Chronic liver disease was the sixth leading cause of death in 2000 and hepatocellular carcinoma (HCC) was the most common cancer in 1997 [21]. According to Liver Disease Prevention & Treatment Research Foundation, there are 3 million people has been affected at a cost of more than US$ 3 million annually in Taiwan. Markov models and decision trees are most commonly used in disease progression simulation.

However, Markov models and decision trees are less able to reflect the clinical appearance more flexibly and alternatively. The risk of disease progression depends on the characteristics of the patients [3]. These models should take age, sex, disease severity, blood type, economical ability, and environmental factors into account simultaneously. Moreover, decisions about when a patient should take more aggressive medicine or when to have an operation are based not only on symptoms but also on social and environmental factors. Variables should be defined to contain factors that change over time to reflect the disease more naturally. Outcomes are costs, disease episodes and symptoms. Sensitivity analyses about cost or transition probabilities should be contained as well [4].

Therefore, this kind of requirement develops a discrete-event computer simulation model for the analysis of HBV disease progression. This paper describes the development of a model to assess the dependencies between a broad range of parameters in the treatment of disease. Discrete-event computer simulation has been widely used inside the management science and operations research contexts since it is already known as an important design tool for versatile applications. Importantly, this kind of simulation has been shown to be a fast and low-cost approach for health management modeling [2, 4]. The individual experience is modeled over time in terms of the events that occur and the consequences of those events. This approach is superior to the traditional Markov models. [3].

DES proceeds very efficiently because the clock is successively advanced to the time when the next event will occur, without wasting effort in unnecessary interim computations [2]. In other words, time advances in ‘discrete’ jumps. By making time explicit, a DES avoids one of the major problems of decision trees [2]. It also enables handling of time that is much more flexible than in Markov models

since there is no need to declare a cycle length. Although cohort Markov models may involve fewer calculations, they require gross oversimplifications making them rarely suitable for informing real decisions.

2. Natural History

Chronic HBV infection is a dynamic process with an early replicative phase and active liver disease and a late low or nonreplicative phase with remission of liver disease. Persistence of HBsAg, hepatitis B e antigen (HBeAg) and HBV-DNA in high titer for more than 6 months implies progression to chronic HBV infection [1]. The variability in chronic hepatitis B has led to its classification into phases of disease based upon alanine aminotransferase (ALT) elevations, the presence of HBeAg, HBV-DNA levels and suspected immune status. The duration of typical HBeAg-positive chronic hepatitis B can be prolonged and severe and may result in cirrhosis [7,16].

Immune tolerance phase:

The presence of circulating HBsAg, HBeAg and high levels of serum HBV-DNA identifies the first immunotolerant phase. Perinatally acquired HBV infection is characterized by a prolonged "immunotolerant" phase with HBeAg positivity, high levels of serum HBV-DNA, normal levels of aminotransferases, minimal liver damage and very low rates of spontaneous HBeAg clearance. A proportion of HBeAg-positive persons, have no ALT elevations and scant histological activity. In Asia, it is most common in children, adolescent, and young adults [11].

Immune clearance phase:

The second immunoactive phase which is associated with a decrease in HBV-DNA concentrations and increased ALT levels and histological activity reflects the host immune mediated lysis of infected hepatocytes [7]. Patients with childhood or adult acquired infection and chronic hepatitis B usually present in the "immunoactive" phase with elevated aminotransferases and liver necroinflammation at histology and approximately 50% will clear HBeAg within 5 years. This phase marks the incubation period of acute HBV infection and lasts about two to four weeks, in contrast with perinatal infection this phase often lasts for decades in which patients with chronic HBV infection has a variable duration from months to years [11]. Hepatitis flares during treatment were defined as elevations in the alanine aminotransferase level to more than twice the baseline level and to more than 10 times the upper limit of normal [13].

Residual phase is the third low or non-replicative phase involves seroconversion from HBeAg to antibody to HBeAg (anti-HBe) usually preceeded by a marked reduction of serum HBV-DNA levels below 105 copies per ml, that are not detecTable Ay hybridization techniques, and followed by normalization of ALT levels and resolution of liver necroinflammation. Serum HBV-DNA remains detectable only by ultrasensitive technique of polymerase chain reaction (PCR) in many patients. In chronic HBV infection this phase is also referred as the inactive HBsAg carrier state. The inactive chronic HBV infection may last for lifetime, but a proportion of patients may undergo subsequent

spontaneous or immunosuppression induced reactivation of HBV replication with reappearance of high levels of HBV-DNA with or without HBeAg seroreversion and rise in ALT levels [11, 16].

HBV can be classified into 7 genotypes A-G and recent studies, all from Asia, have indicated that HBV genotype B is associated with earlier HBeAg seroconversion than genotype C, thus most likely explaining the less progressive disease in patients with genotype B [6, 8, 19]. HBeAg seroconversion associated with liver disease remission marks the transition from chronic hepatitis B to the inactive HBsAg carrier state, however a small percentage of patients (approximately 5%) may continue to show biochemical activity and high levels of serum HBV-DNA at the time of HBeAg seroconversion [1, 12, 14]. These patients as well those undergoing reactivation of hepatitis B after HBeAg seroconversion may generate the group of patients with HBeAg negative chronic hepatitis B.

Figure 1 presents a model with a slight modification by Liaw and Chu [27]. Here we take numerical experiments based on Figure 1 by some required approximations and modifications stated in the following. First, we assume that several estimates in Figure 1 are annual transition probabilities rather than percentages. Second, the state "curative therapy" is combined with the state "death/transplantation." and replaced with the state "death". Besides, no treatments are applied to patients. Third, in Figure 1, the annual transition probability from "HBeAg(+) hepatitis HBV-DNA> $2\times10^{6\sim7}$ IU/ml" to "HBeAg(+) hepatitis HBV-DNA> $2\times10^{4\sim5}$ IU/ml" and "HBeAg seroconversion" is assumed to be 15% per year.

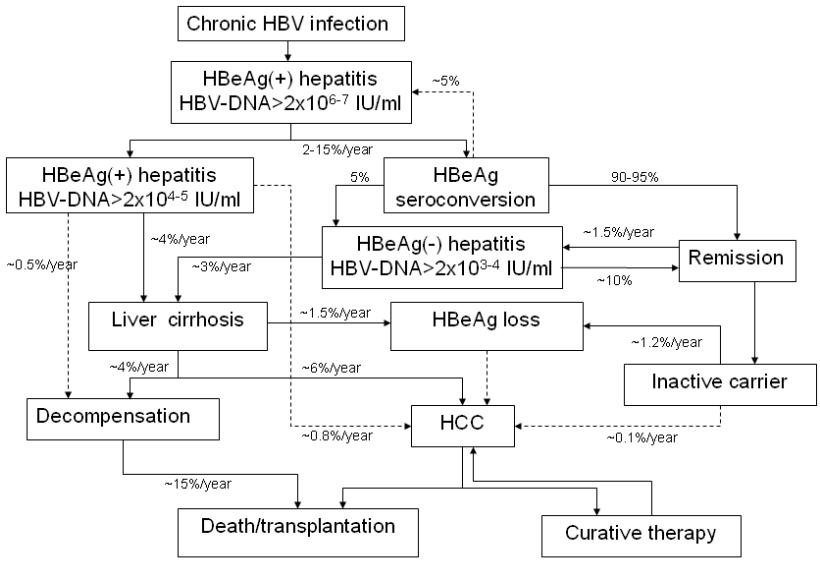

Figure 1: A transition diagram of chronic HBV progression from Liaw and Chu [27].

The outward annual transition probability from state "HBeAg(+) hepatitis HBV-DNA> $2\times10^{6\sim7}$ IU/ml" is assumed to be 15% per year. We may assume that the ratio between transitions to "HBeAg(+) hepatitis HBV-DNA> $2\times10^{4\sim5}$ IU/ml" and transitions to "HBeAg seroconversion" is approximately 2:1. In other words, annual transition probability to "HBeAg(+) hepatitis HBV-DNA> $2\times10^{4\sim5}$ IU/ml" is

10% per year and annual transition probability to “HBeAg seroconversion” is 5% per year. Figure 2 summarizes the modifications.

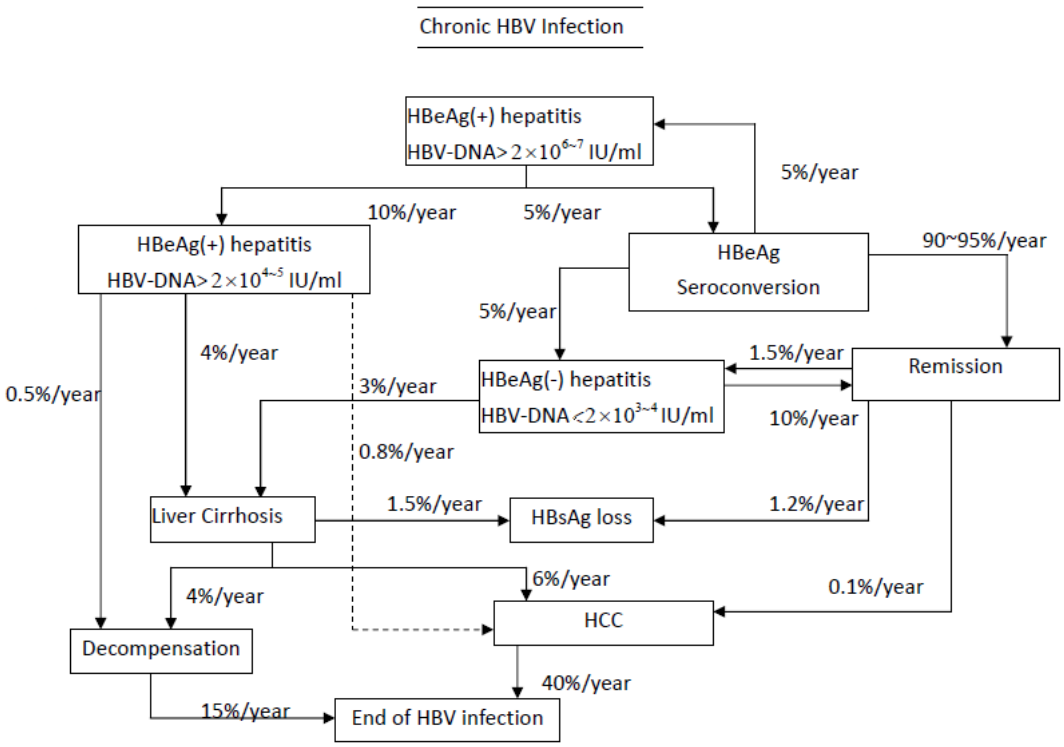

Figure 2: The modified transition diagram of Chronic HBV progression.

In Figure 2, consider a random variable sequence $X=\{X_n, n\in \mathrm{N}\}$ and $T=\{T_n, n\in \mathrm{N}\}$ defined on a probability space (Ω, F, P) with a finite set $E=\{s_1, s_{2,}, \cdots, s_m\}$, $m\in \mathrm{N}$, where N is the set of all positive integers. For example, s_1 denotes the health status of HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL; s_2 denotes the health status of HBeAg(-) hepatitis HBD-DNA> $2\times10^{3\sim4}$ IU/mL, and so on. X_n represents the state at the n^{th} transition and T_n denotes the time before the n^{th} transition. If $X_n=i$ and $i\in E$, then the process is said to be in state i at time n. For any nonnegative integer n and any state $i, j, i_0, \cdots, i_{n-1}$, we have:

$$p_{i,j}=P(X_{n+1}=j \mid X_0=i_0, X_1=i_1, \cdots, X_{n-1}=i_{n-1}, X_n=i)=P(X_{n+1}=j \mid X_n=i).$$

In addition, if state j is not adjacent to state i in the HBV disease progression model, then the probability $p_{i,j}$ is assumed to be 0. We define

$$p_i=\sum_{j=1}^{m} p_{i,j},$$

where p_i denotes the probability for a patient to leave state i in one year.

3. Gompertz Distributions

The principal focus of the analysis was to determine the relative transitions of hepatic liver disease in patients with clinical symptoms. An analysis with best estimates for all model parameters and event probabilities was carried out from a societal perspective following the consensus recommendations of

Liaw and Chu [27]. Instead of the conventional Markov Model in most published papers on such outcome studies, the methodology is to use discrete event simulation for prognosis of HBV modeling. The model tracks the liver disease status, virus activity, clinical symptoms, and age of each patient. Survival life is predicted on the basis of disease extent.

The celebrated Gompertz distribution [18] is introduced in the DES model. We assume that each state i follows the Gompertz distribution with different parameters a_i and b_i. The probability density function of Gompertz distribution is given as

$$f_i(t;\ a_i,\ b_i) = b_i \cdot e^{a_i t} \exp[\frac{b_i}{a_i}(1-e^{a_i t})]$$

for $0 < t < \infty$, $a_i > 0$, and $b_i > 0$ (0 otherwise). The corresponding cumulative distribution function is

$$F_i(t;\ a_i,\ b_i) = 1-\exp[\frac{b_i}{a_i}(1-e^{a_i t})].$$

In every state, it is essential to estimate the time interval of such a health state in simulation. Denoting by T the time interval of a specific state i, the probability of an incidence occurrence before time t where $T \le t$ is

$$P(T_{n+1}-T_n \le t|\mathrm{X}_n = i,\ X_{n+1} \ne i) = F_i(t;\ a_i,\ b_i) = 1-\exp[\frac{b_i}{a_i}(1-e^{a_i t})]. .$$

In particular, for every state i, the probability of an incidence occurrence within one year is $T \le 1$. Hence, we have

$$P(T_{n+1}-T_n \le 1|\mathrm{X}_n = i,\ X_{n+1} \ne i)) = 1-\exp[\frac{b_i}{a_i}(1-e^{a_i})] = p_i.$$

For given transition probability p_i and a_i in state i, we have b_i as a function of a_i written as

$$b_i = f(a_i) = \frac{a_i \ln(1-p_i)}{1-e^{a_i}}.$$

In DES, the average length of time intervals of the nonabsorbing state is estimated by $1/p_i$. For each simulation run, we converted all available data into annual probability estimates for use in the DES model. We calculated these annual estimates of each time period that a state will experience. Hence, we know that

$$P(T_{n+1}-T_n \le t|\mathrm{X}_n = i,\ X_{n+1} \ne i) = F_i(t;\ a_i) = 1-\exp[\frac{\ln(1-p_i)}{1-e^{a_i}}(1-e^{a_i t})].$$

According to Yousef [18], the mean $u_t|_i$ of the distribution is

$$u_t|_i = \frac{1}{a_i} e^{\frac{b_i}{a_i}} \left[\ln a_i - \ln b_i - \gamma - \sum_{k=1}^{\infty} \frac{\left(-\frac{b_i}{a_i}\right)^k}{k \cdot k!} \right],$$

where $\gamma \sim 0.5772$ is an Euler's constant. Hence, the equation of $u_t|_i$ for each status can be rewritten as

$$u_t\,|_i = \frac{1}{a_i} e^{\frac{\ln(1-p_i)}{1-e^{a_i}}} \left[\ln \frac{1-e^{a_i}}{\ln(1-p_i)} - \gamma - \sum_{k=1}^{\infty} \frac{\left(-\frac{\ln(1-p_i)}{1-e^{a_i}} \right)^k}{k \cdot k!} \right].$$

We want to choose proper a_i for each state to fit that $u_t\,|_i \approx 1/p_i$, so we solve the equation $u_t\,|_i - 1/p_i = 0$ for a_i for different status. Table 1 summarizes the results of a_i and b_i. Note that the status "Death/Transplantation" is the absorbing state. In addition, for the state "HBeAg seroconversion", every patient in this symptom is assumed to stay for one year and then transfers to another states. For patients at "HBsAg loss", he will follows the population mortality instead of the Gompertz distribution.

Table 1: The symbols and parameters a_i and b_i of states in Figure 2.

Symptoms	State symbol	a_i	b_i
HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL	s_1	0.11	0.0004
HBeAg(+) hepatitis HBD-DNA> $2\times10^{4\sim5}$ IU/mL	s_2	0.4	0.0001
HBeAg seroconversion	s_3	None	None
HBeAg(-) hepatitis HBD-DNA< $2\times10^{3\sim4}$ IU/mL	s_4	0.095	0.0004
Remission	s_5	0.02	0.0001
Liver cirrhosis	s_6	0.081	0.0003
HBsAg loss	s_7	None	None
Decompensation	s_8	0.11	0.0004
HCC	s_9	0.28	0.0011
Death/Transplantation	s_{10}	None	None

4. Model Overview

To articulate the natural course of chronic HBV, a discrete-event simulation model was developed with the ProModel [20]. This model is based on the concepts of entities, locations, processes, time of events and attributes. In this study, an entity represents a patient in the disease progression. Locations are liver status where the processes are the routines that connect locations. Processes will decide how an entity will work in every location, where the Gompertz distribution [18] and the life table [22] are embedded. Attributes are the possible clinical symptoms of patients which are presented by entities. These elements, taken together with discrete time of every possible events of a system, allow for the construction of computer models that represent the system actual operating conditions. Basic system parameters are excerpted from the literature given in Liaw and Chu [27], and the life table [22] is described in Appendix.

We developed a Discrete Event Simulation model based on the natural course of Chronic HBV [9, 16, 27]. In this section, the proposed DES model will be expounded in detail. Flow diagram of the computation process for a discrete event simulation is also discussed. The life table [22] is also concluded in the DES model, which is given in Appendix.

4.1 Entities

A central component of DES is the entity which denotes the patient in modeling. In contrast to decision trees and Markov models, which do not specify the patient but instead focus exclusively on outcomes or states, the patient is an explicit element in a DES. A DES model allows introducing interactions between patients or different status while a Markov Monte-Carlo microsimulation deals with one health status at a time. It is important while modeling for infectious diseases.

Patients have attributes of which individual has a specific value for each characteristic. These values are defined at the start of the simulation and updated at particular points in time. Two important attributes of patients are the time to reach the significant status and the sojourn time in status. When patients start infected with HBV, they are concerned about how much time they have to reach the worse status, how much time they could stay healthy, what the remaining life expectancy is for them, or what the survival probability is in the future. Attributes in DES play an important part in estimating.

4.2 Locations

The model contains ten liver statuses as in Table 1: HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL, HBeAg(+) hepatitis HBD-DNA> $2\times10^{4\sim5}$ IU/mL, HBeAg seroconversion, HBeAg(-) hepatitis HBD-DNA> $2\times10^{3\sim4}$ IU/mL, remission, liver cirrhosis, HBsAg loss, decompensation, hepatocellular carcinoma, and death/transplantation. Each liver status is defined as a location in this model. All patients begin in the Chronic HBV infection and enter HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL immediately. Patients change to any of the liver statuses with given probability according the Gompertz function. When entities entered a location, they will follow the rule of processing defined on each location to decide how long they would stay in this location and where to go for the next. A demonstration of DES model is shown as Figure 3.

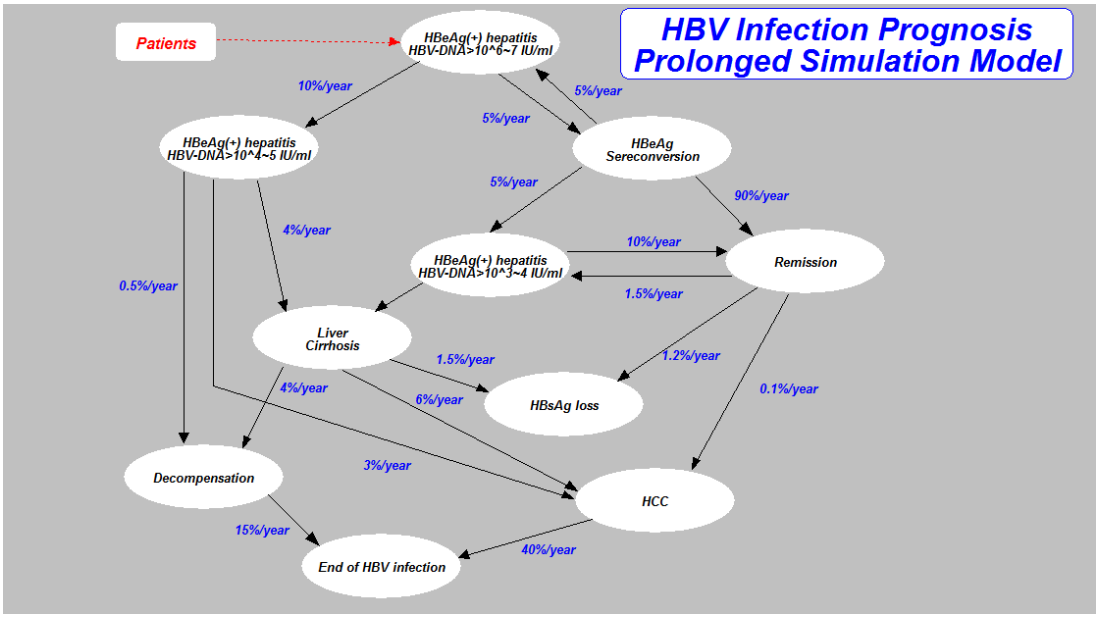

Figure 3: A demonstration of DES model

4.3 Processing

Processing guides how an entity acts in a location. Figure 4 shows how a patient will move in this DES disease progression. First, a HBV patient is created and then he starts his own HBV disease progression. Generally speaking, an entity will reach the status "HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL". Then the entity will decide how long he will stay at the state "HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL" according to the Gompertz function given in Section 5. For a entity at this status, given a random number $0 \le r \le 1$, we have the waiting time T_1 for this patient at this state by

$$T_1 = \frac{1}{a_1}\ln(\ln\frac{e}{(1-r)^{1-e^{a_1}/\ln(1-p_1)}}).$$

That is, this patient will spend time T_1 at current state. After waiting time T_1 in the state "HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL" for a while, the entity will decide whether he will die or not according to the population mortality or disease progression. If the entity died, then he simply reaches the final status "Death". If the entity does not die, he will leave the current state and reach another state s_j, $j \sim i$. Then the entity repeats the progression rule for another state s_j again until he reaches the final state "Death".

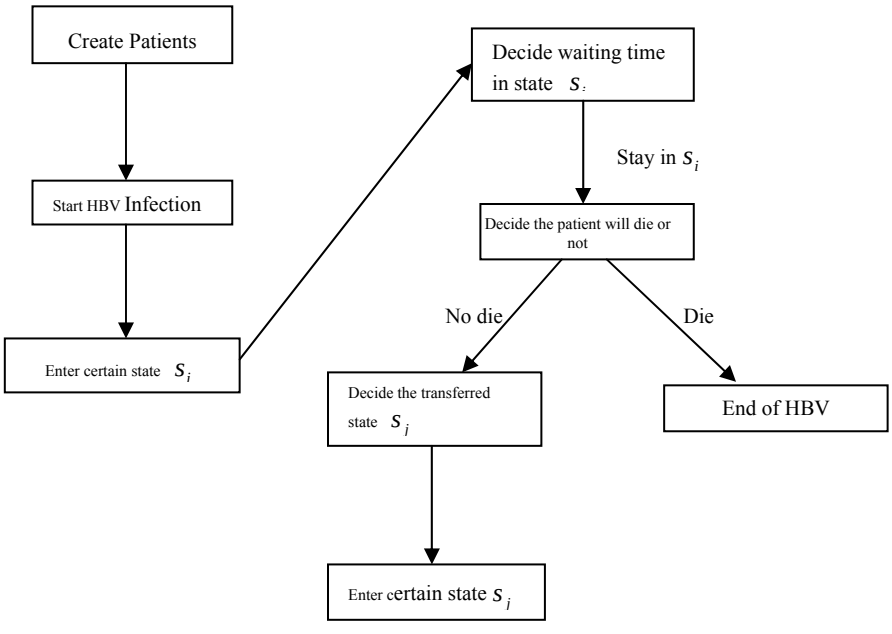

Figure 4: The flow chart of the DES disease progression.

5. The Outcome of DES Model

5.1 The outcome of DES model

This process continues until a predetermined time is reached, at which point the simulation is terminated. The basic model includes only a generic setting and no treatment strategy. The model is effective by simulating cohorts of hypothetical patients while tracking disease progression, complications, and survival. For each set of model assumptions under consideration, we may simulate hypothetical cohorts of patients.

The model tracks up to 10 individual hepatic clinical symptoms in each patient, specifying and updating liver disease status shown in Table 1. Percentages of occurrences at different liver status are given in Figure 2. For each hypothetical patient, the type of virus activity is chosen at random from a population distribution conditioned on a previous liver status and other variables. The type of virus activity is then distributed throughout the simulation. We assume that each patient has an independent, equal probability of being infected by virus**.** The clinical symptom of each patient is similarly selected at random from a population distribution but mainly depending on the previous condition. We assume time advances with Gompertz distributions and that no new liver disease develops between any two occurrences, since all events are assumed to happen at discrete time manner. Events can happen in any logical sequence and even simultaneously. They can recur if that happens in reality and they can change the course of a given patient's experience by influencing that patient's attributes and the occurrence of future events with no restriction on 'memory'.

In the DES, the model is assumed to have a lifetime horizon and a cycle length of 75 years with patients with HBV at age 25. In ProModel, one year is assumed to be 360 days, so we setup the time limit to be $75 \times 360 = 27000$ days. Note that the unit of the results is days. The simulation is repeated for 10 times, and in every simulation 20000 patients are involved. The simulated results are shown in Figure 5.

Variable Name	Total Changes	Average Hours Per Change	Minimum Value	Maximum Value	Current Value	Average Value	
remission time*	8880.6	3.03	0.69	25919.5	13776.6	4831.26	(Average)
remission time*	129.30	0.04	0.84	313.71	4938.26	90.49	(Std. Dev.)
e loss time*	6784.1	2.15	365	365	365	365	(Average)
e loss time*	71.86	0.34	0	0	0	0	(Std. Dev.)
decompensation time*	4942	5.42	0.45	10934.9	3806.35	2400.5	(Average)
decompensation time*	86.77	0.09	0.32	12.61	2715.02	24.00	(Std. Dev.)
cirrhosis time*	10924	2.46	0.21	10942.6	2108.21	2754.7	(Average)
cirrhosis time*	99.49	0.02	0.22	5.28	1137.31	22.45	(Std. Dev.)
DNA1034 time*	4628.4	5.82	0.75	10937.3	3256.45	2604.57	(Average)
DNA1034 time*	114.03	0.14	0.46	11.36	2957.59	26.53	(Std. Dev.)
DNA1045 time*	13441.5	1.65	0.19	10945.7	9643.12	3966	(Average)
DNA1045 time*	72.97	0.08	0.18	3.66	807.24	22.76	(Std. Dev.)
HCC time*	7789.7	3.44	0.48	10936.9	2530.07	2162.96	(Average)
HCC time*	58.67	0.03	0.39	11.49	4026.27	24.65	(Std. Dev.)
sloss time*	4661.4	5.79	365	25258	18469	11424.7	(Average)
sloss time*	86.69	0.10	0	335.41	3025.56	91.99	(Std. Dev.)
DNA1067 time*	20337.4	0.76	0.08	10838.5	9350.77	1979.67	(Average)
DNA1067 time*	12.60	0.11	0.07	90.59	1381.96	6.92	(Std. Dev.)
time 2 DNA1045*	13441.5	1.65	2.85	15246.5	12667.8	2023.43	(Average)
time 2 DNA1045*	72.97	0.08	0.09	1695.3	1397.07	11.31	(Std. Dev.)
time 2 DNA1034*	4628.4	5.82	376.98	26266.4	14561	6648.72	(Average)
time 2 DNA1034*	114.03	0.14	6.22	436.95	10504.6	90.68	(Std. Dev.)
time 2 DNA1067*	20337.4	0.76	1	1	1	1	(Average)
time 2 DNA1067*	12.60	0.11	0	0	0	0	(Std. Dev.)
time 2 HCC*	7789.7	3.44	165.99	26318.9	24307.3	8268.19	(Average)
time 2 HCC*	58.67	0.03	76.35	368.78	4071.7	33.37	(Std. Dev.)
time 2 decompensation*	4942	5.42	253.8	25383.3	22995.2	8259.16	(Average)
time 2 decompensation*	86.77	0.09	93.94	583.24	2868.77	74.37	(Std. Dev.)
time 2 cirrhosis*	10924	2.46	61.96	25639.1	24771.3	6379.1	(Average)
time 2 cirrhosis*	99.49	0.02	34.14	650.03	1101.41	38.73	(Std. Dev.)
time 2 eloss*	6784.1	2.15	3.03	7661.08	3004.72	1951.19	(Average)
time 2 eloss*	71.86	0.34	0.23	383.03	755.08	18.34	(Std. Dev.)
time 2 sloss*	153932	0.17	472.56	26592.2	9441.76	7331.55	(Average)
time 2 sloss*	2985.81	0.00	125.83	34.23	4471.74	50.30	(Std. Dev.)
time 2 remission*	8880.6	3.03	369.12	14833.5	1934.34	2504.89	(Average)
time 2 remission*	129.30	0.04	0.24	736.14	1009.92	21.98	(Std. Dev.)
time to death*	19134.3	1.41	21.21	26995.4	26995.4	13070.5	(Average)
time to death*	24.59	0.00	12.68	4.18	4.18	53.37	(Std. Dev.)

Figure 5: The results of the HBV disease progression model.

From Figure 5, there are the results of the HBV disease progression model. The results are classified into 2 parts. Take the status "remission" for example, one is the word "remission time", and the other is "time 2 remission". "Remission time" represents the time a patient spent in status remission, whereas "time 2 remission" means the time a patient spent before reaching the status "remission" for the first time. The time unit in Figure As the titles in Figure 5, we focus on the average value. The average value for "remission time" is 4831.26 days, and 90.49 days is the standard deviation for the results. The average value for "Time 2 remission" is 2504.89 days with standard deviation 21.98 days. In other words, the average value for "remission time" and "Time 2 remission" is 4831.26/360=13.42 years and 2504.89/360=6.96 years respectively. Table 2 summarized the results of Figure 5. Note that the time unit in Figure 5 is days, and the time unit in Table 2 is years.

Table 2: The average sojourn time in different liver status and the average time to reach different liver status in Figure 2

Symptoms	The average sojourn time	The average time
HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL	5.50 years	None
HBeAg(+) hepatitis HBD-DNA> $2\times10^{4\sim5}$ IU/mL	11.02 years	5.62 years
HBeAg seroconversion	1 year	5.42 years

HBeAg(-) hepatitis HBD-DNA> $2\times10^{3\sim4}$ IU/mL	7.23 years	18.46 years
Remission	13.42 years	6.96 years
Liver cirrhosis	7.65 years	17.72 years
HBsAg loss	31.74 years	20.37 years
Decompensation	6.67 years	22.94 years
HCC	6.01 years	22.97 years
Death	None	36.31 years

This model was constructed by a systematic search of the literature to identify source materials on the natural history, epidemiology of HBV, and demography. In the state transition model, patients with HBV may remain in that state, move on to more progressive stages of liver disease or may clear the disease. The model has a lifetime horizon and a cycle length of 75 years, assuming a patient with HBV at age 25. Table 2 demonstrates the average sojourn time in each liver status and the average time for a patient at age 25 to reach different liver status. The patients are estimated to wait 7.65 years at the liver status liver cirrhosis and 31.74 years at HBsAg loss respectively. Moreover, it is approximated about 17.72 years for a patient at age 25 to reach the liver status liver cirrhosis. The remaining life expectancy is predicted about 36.31 years for a patient at age 25 at the beginning of HBV infection. The outcomes analysis of our study presents a byproduct of the development of DES, which illustrates the usage of DES.

5.2 DES versus Markov

In this section, we compare the results of a DES model and a Markov model for chronic HBV disease progression. The results are based on assuming that the patients are at state s_1 starting at age 25. Table 3 represents the outcome of a DES model and Table 4 shows the result of a Markov model.

Table 3: The simulated disease progression probabilities distribution for a DES model

States / Ages	s_1	s_2	s_3	s_4	s_5	s_6	s_7	s_8	s_9	s_{10}
25	1	0	0	0	0	0	0	0	0	0
30	0.4864	0.3059	0.0308	0.0130	0.1104	0.0306	0.0061	0.0044	0.0072	0.0054
35	0.1452	0.4126	0.0177	0.0367	0.1814	0.1028	0.0308	0.0200	0.0312	0.0221
40	0.1448	0.4126	0.0177	0.0367	0.1814	0.1030	0.0308	0.0196	0.0312	0.0221
45	0.0065	0.2146	0.0007	0.0623	0.1273	0.1667	0.1137	0.0570	0.0877	0.1637
50	0.0036	0.1202	0.0006	0.0540	0.0931	0.1426	0.1534	0.0590	0.0872	0.2872
55	0.0005	0.0135	0.0002	0.0340	0.0425	0.0699	0.2054	0.0410	0.0562	0.5370
60	0.0001	0.0023	0	0.0231	0.0327	0.0381	0.2094	0.0273	0.0349	0.6320
65	0	0.0007	0	0.0148	0.0266	0.0181	0.2014	0.0159	0.0187	0.7039
70	0	0.0003	0	0.0091	0.0221	0.0093	0.1814	0.0094	0.0091	0.7593
75	0	0.0002	0	0.0056	0.0188	0.0047	0.1497	0.0049	0.0040	0.8122
80	0	0.0001	0	0.0040	0.0141	0.0023	0.1101	0.0025	0.0019	0.8659

Table 4: The simulated disease progression probabilities distribution for a Markov model

States / Ages	s_1	s_2	s_3	s_4	s_5	s_6	s_7	s_8	s_9	s_{10}
25	1	0	0	0	0	0	0	0	0	0
30	0.4479	0.3275	0.0263	0.0096	0.1379	0.0289	0.0034	0.0047	0.006	0.0078
35	0.201	0.3948	0.0118	0.0185	0.2075	0.076	0.0173	0.0166	0.0158	0.0407
40	0.09	0.3639	0.0053	0.0233	0.225	0.1044	0.0367	0.0279	0.0218	0.1017
45	0.0401	0.3031	0.0024	0.0251	0.2206	0.1122	0.0578	0.0345	0.0234	0.1808
50	0.0178	0.2399	0.001	0.0249	0.2072	0.106	0.0778	0.0363	0.0222	0.2669
55	0.0078	0.1841	0.0005	0.0237	0.1901	0.0926	0.0952	0.0343	0.0194	0.3524
60	0.0034	0.1375	0.0002	0.0217	0.1707	0.0763	0.1086	0.0299	0.016	0.4358
65	0.0015	0.1	0.0001	0.0193	0.15	0.0599	0.1171	0.0245	0.0126	0.5151
70	0.0006	0.07	0	0.0164	0.1272	0.0447	0.1187	0.0189	0.0094	0.5941
75	0.0002	0.0463	0	0.0133	0.1022	0.0312	0.1119	0.0134	0.0066	0.6748
80	0.0001	0.0282	0	0.0098	0.0755	0.0199	0.0955	0.0087	0.0042	0.7582

Table 3 and Table 4 show the simulated disease progression probabilities distribution. After ten years, about 14.52% it will be in s_1 and 18.14% in s_5, and 2.2% in s_{10} in a DES model, whiles about 9% it will be in s_1 and 20.75% in s_5, and 4% in s_{10} in a Markov model. Likewise, the other probabilities can be interpreted in the same manner. Figure 6 and Figure 7 show the corresponding survival probability simulated from a DES and a Markov model respectively. Moreover, the remaining life expectancy for DES model and Markov model are 36.31 years and 39.48 years.

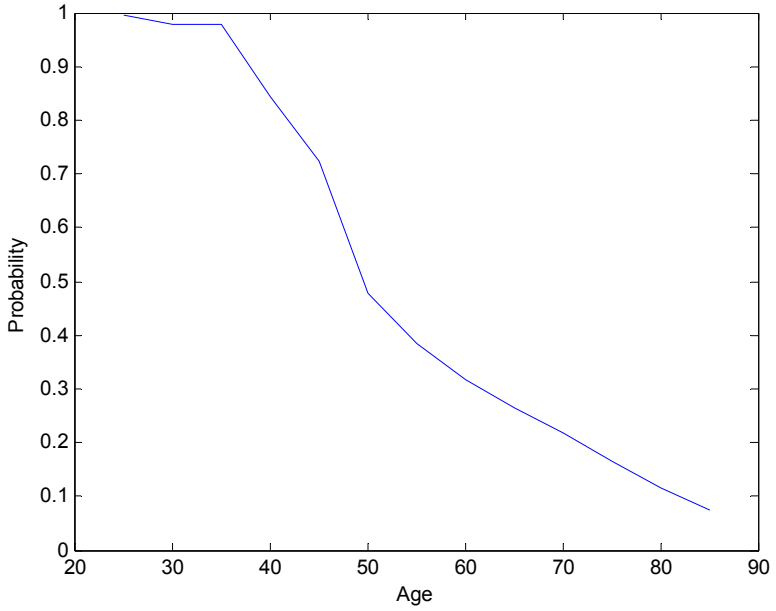

Figure 6: The survival probability of different ages starting at age 25

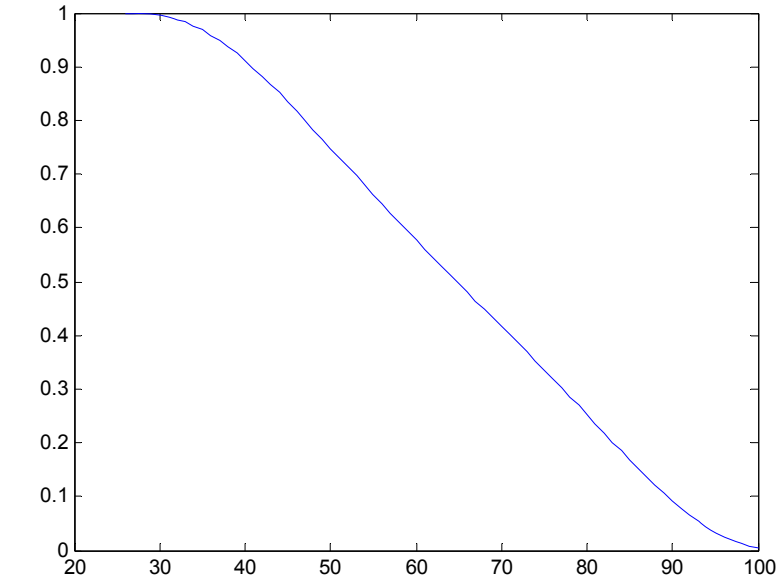

Figure 7: The survival probability of different ages starting at age 25

6. Conclusion

A model of DES is a tool for decision support system. The key feature of any decision model is to be "fit for purpose" for decision-making [25]. A model is a logic mathematical framework that permits the integration of facts and values and that links these data to outcomes for decision makers. If a model built at human disease processes to reasonably inform decision-makers and deal with uncertainty, variability, and heterogeneity, interaction, etc., simulation can appropriately handle the realities to correctly model it at the required depth, although it may involve a large number of computations which may be a hindrance to conducting DES. However, as computing techniques emerge dramatically, DES becomes easy and powerful for various managerial purposes.

Our analysis has two strengths. First, to our knowledge, our study is the first discrete event simulation model of decision analysis to compare competing strategies for chronic HBV infection. Previous models have focus on either the Markov model or decision tree analysis. Second, our model acknowledges the increasing prevalence of simulation models. This approach increases the generalizability of modeling flexibility in light of statistical data.

Our study only demonstrates a possible construction for a DES used in analysis of chronic HBV. Our model has several limitations. First, several of our estimates are based on literature which may depend on different design, patient population, follow-up and quality. Our estimates of patient health preferences may be limited because we adopted utilities for cirrhosis health states in HBV from limited sources. However, it is reasonable to assume that a patient who develops cirrhosis or related complications would have the same quality of life decrement regardless of time. Second, the time period of health states were estimated and adjusted accordingly to systematical consistence of simulation. More conditional health statuses could be included for better results and decision-making processes.

7. Acknowledgements

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科技部補助專題研究計畫執行國際合作與移地研究心得報告

日期：__年__月__日

計畫編號	MOST 103-2221-E-004 -003 -		
計畫名稱	離散事件模擬法與慢性肝病進程之預測(I)		
出國人員姓名	陸行	服務機構及職稱	政大應數系
出國時間	104 年 8 月 25 日 至 104 年 9 月 15 日	出國地點	馬來西亞吉隆坡
出國研究目的	□實驗 □田野調查 □採集樣本 ■ 國際合作研究 □使用國外研究設施		

一、執行國際合作與移地研究過程

因為研究計畫需要，必須到馬來西亞的 Monash University Malaysia 從事資料收集和交換研究心得等等的國際合作研究工作。移地研究從 104 年 8 月 25 日至 9 月 15 日總共 22 天。若能成行，必可增強研究成果，促成國際合作和論文發表，故需要延長計畫至 104 年 9 月 30 日。

國際合作和訪問的對象是 Dr. Kenneth Lee and Dr. David Wu。他們協助我開發模擬計算模式和比較模擬結果。因為他們對於亞洲人與馬來西亞人在使用藥物和經濟成本效益之特質和分析的經驗，以及比較了解相關文獻與資料。我向他們學習後，開發 TreeAge 的模擬程式，如後頁所示，作為研究論文的 Appendix。以 Appendix 的內容當作本計畫案之參考模型，由此，我可以將離散事件模擬法的計算結果與其比較和調整模式，使其更符合實際的意義。

二、研究成果

業經反覆討論與計算，和參考實務工作者，如長庚醫院的醫師，以及研究夥伴藥物經濟學家鄭力仁博士的意見後，離散事件模擬法之開發已顯效力，其計算結果也受專家與臨牀醫生認同，TreeAge 的計算結果與本計畫案的計算結果亦趨於一致。

三、建議

感謝科技部給本人這個跨領域研究的機會，因為這個研究工作牽涉數學模式與理論、工程程式與工具開發撰寫、公共經濟與衛生專家、統計學家和臨牀專業醫生等不同背景的知識，本人是一邊學一邊做。同時感謝不同領域專家的協助，讓計畫得以進行。希望科技部繼續支持此類研究案。但是，本計畫原定三年完成，卻只獲得一年補助。所以這一年只做到模式開發與比較，無緣繼續做參數最佳化分析和成本效益分析。

未來，這個模式仍要繼續開發，同時也透過政大，希望建立與 Monash University Malaysia 的合作互訪機制，持續努力完成離散事件模擬法在藥物經濟成本效益分析的決策支援系統模型。

四、本次出國若屬國際合作研究，雙方合作性質係屬：(可複選)

□分工收集研究資料
□交換分析實驗或調查結果
■共同執行理論建立模式並驗証
■共同執行歸納與比較分析
□元件或產品分工研發
□其他 (請填寫) _____

五、其他

Appendix

A Chronic Hepatitis B Virus Infection Model on TreeAge

We use the software TreeAge [24] as a computing tool to compare results of the HBV disease progression with that calculated by the proposed model in this paper. The Markov model in TreeAge [24] is shown as a tree in Figure A. The transitional probabilities between symptoms are defined in the first box of the tree based on Figure 2. For each Markov node, first it will decide that whether or not the patient will die by population mortality or disease progression. If the patient died, then the disease progression will end up with death; if the patient does not die of population mortality, then the patient will make a transfer to another state or simply stay at the previous state. In Figure A, the symbols pDie, pDieDecompensation, and pDieHCC represent the population mortality, the probabilities of death at state decompensation and at state HCC respectively. Besides, pDNA1067_DNA1045 means the transitional probability from state "HBeAg(+) hepatitis HBV-DNA $> 2 \times 10^{6\sim7}$ IU/ml" to "HBeAg(+) hepatitis HBV-DNA$> 2 \times 10^{4\sim5}$ IU/ml". The interpretations for the other transition probabilities are similar. The symbol "#" represents the probability of one subtracting the total probabilities of other transitions above. Note in the first block named "HBV problem", pDie is defined to be that calculated by one subtracting the survival probability in the life table at different ages.

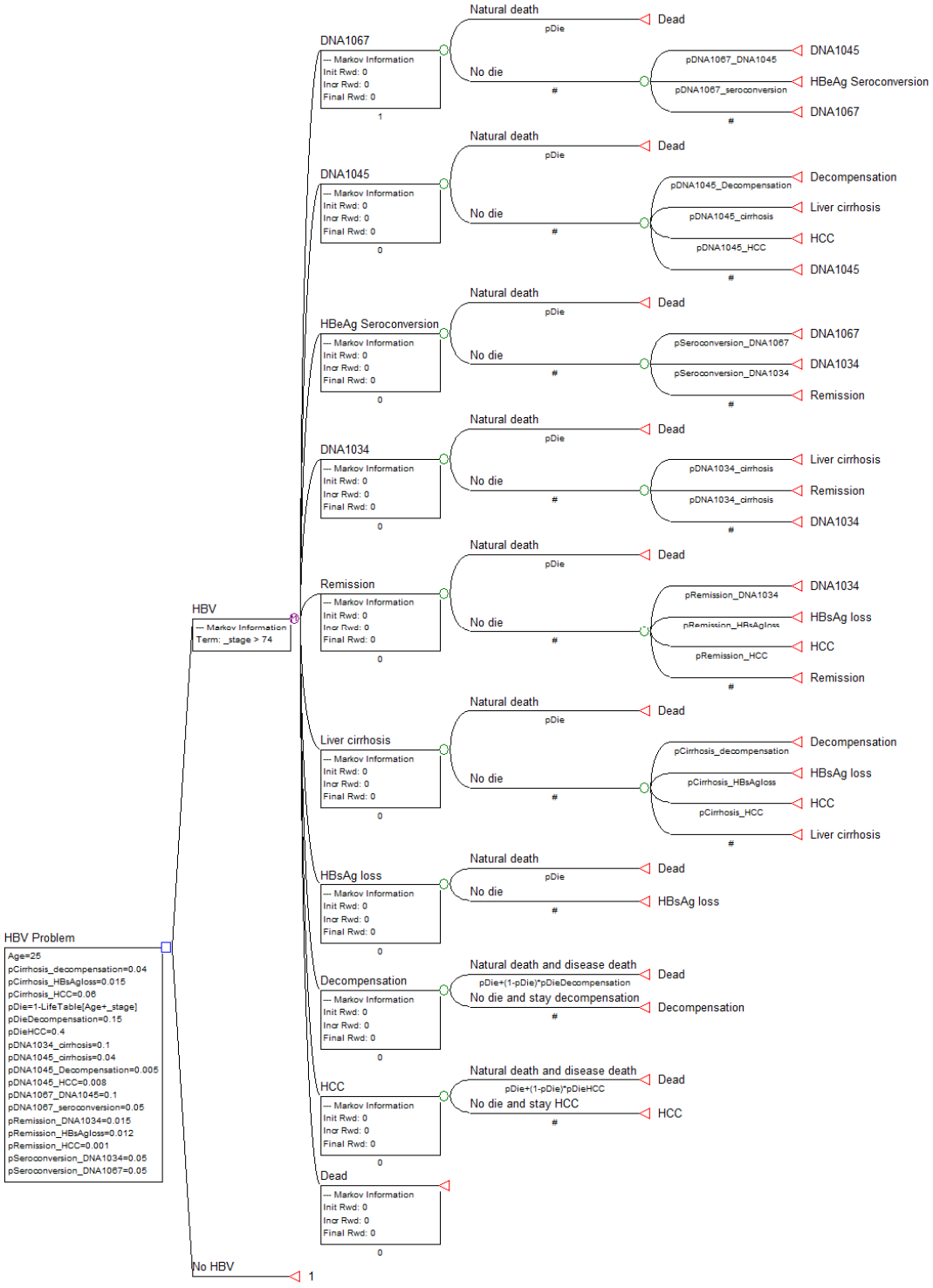

Figure A: The HBV disease progression model in TreeAge.

The survival probability at different ages in Table A is applied to the Markov model with TreeAge as well. Table A shows the simulated disease progression probabilities distribution, which is similar to the result in Table A. The simulated disease progression probability distributions are plotted in Figure B. Moreover, the corresponding survival probability can be computed simultaneously. Figure D shows the

survival curve for the patients infected HBV starting at age 25.

Table A: The simulated disease progression probabilities distribution by using TreeAge

States / Ages	s_1	s_2	s_3	s_4	s_5	s_6	s_7	s_8	s_9	s_{10}
25	1	0	0	0	0	0	0	0	0	0
30	0.4478	0.3274	0.0263	0.0087	0.1378	0.0298	0.0034	0.0047	0.0060	0.0081
35	0.2009	0.3946	0.0118	0.0148	0.2063	0.0795	0.0174	0.0169	0.0162	0.0417
40	0.0899	0.3635	0.0053	0.0170	0.2216	0.1100	0.0371	0.0287	0.0225	0.1046
45	0.0400	0.3024	0.0023	0.0171	0.2142	0.1189	0.0582	0.0358	0.0243	0.1867
50	0.0177	0.2392	0.0010	0.0161	0.1975	0.1130	0.0782	0.0378	0.0232	0.2763
55	0.0078	0.1831	0.0005	0.0146	0.1773	0.0991	0.0953	0.0358	0.0203	0.3662
60	0.0034	0.1363	0.0002	0.0129	0.1554	0.0820	0.1080	0.0314	0.0168	0.4537
65	0.0014	0.0986	0.0001	0.0110	0.1328	0.0646	0.1154	0.0258	0.0132	0.5371
70	0.0006	0.0684	0.0001	0.0091	0.1091	0.0482	0.1155	0.0198	0.0099	0.6197
75	0.0002	0.0447	0.0000	0.0070	0.0844	0.0336	0.1069	0.0140	0.0068	0.7023
80	0.0001	0.0265	0.0000	0.0050	0.0595	0.0212	0.0888	0.0089	0.0043	0.7857

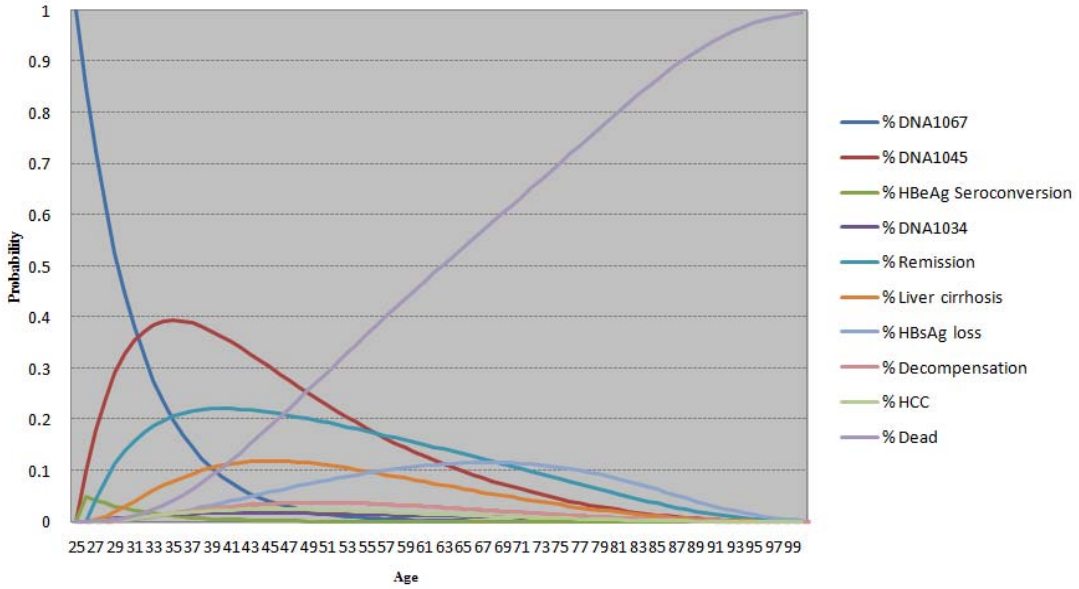

Figure B: Starting from s_1, the simulated disease progression with probabilities at different states by using TreeAge

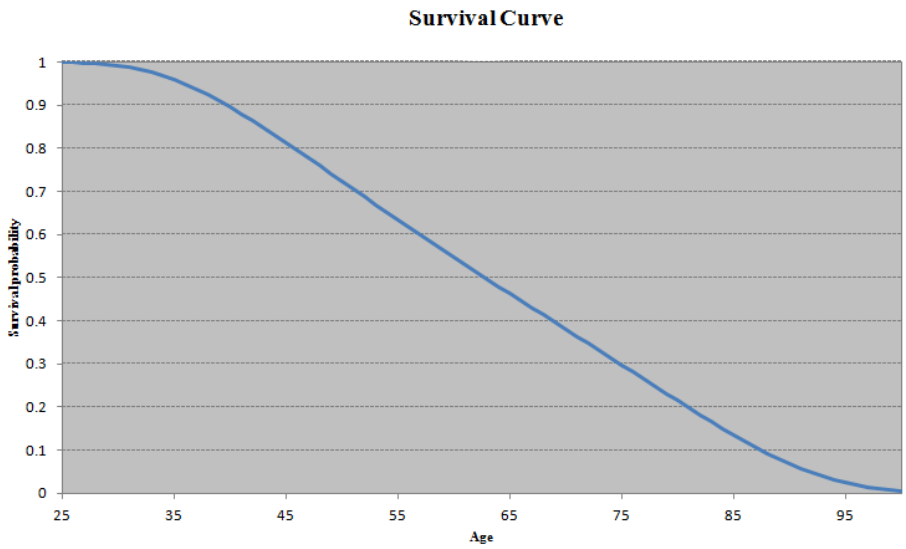

Figure C: The survival curve starting from s_1 computed by using TreeAge

科技部補助專題研究計畫出席國際學術會議心得報告

日期：__年__月__日

計畫編號	MOST 103-2221-E-004 -003 -		
計畫名稱	離散事件模擬法與慢性肝病進程之預測(Ⅰ)		
出國人員姓名	陸行	服務機構及職稱	政大應數系
會議時間	103 年 11 月 9 日 至 103 年 11 月 12 日	會議地點	美國舊金山
會議名稱	(中文) 作業研究和管理科學 2014 年會 (英文) INFORMS Annual Meeting 2014		
發表題目	(中文) 安全檢查系統的等候時間計算研究 (英文) Computing the Waiting Time in a Security Check System		

一、參加會議經過

林蔚君博士是 INFORMS 美國作業研究和管理科學會的國際部的負責人，她希望為臺灣同時也為 INFORMS 努力創造更多的國際聯繫，因此計畫在 INFROMS 的 2014 年會中推銷兩份臺灣主導的國際期刊 Journal of industrial and production engineering (JIPE) 和 International Journal of Operations Research (IJOR)，期待增加更多的學術影響力。於是由張國皓教授、林東盈教授、王逸琳教授和我組織一個場次，特別報告臺灣相關的學術論文。

這是一個超大型的學術會議，據主辦單位估計有將近 5500 人參加這個會議，會議共舉行四天。我們的場次在星期一，參加的人除了對論文主題有興趣的人外，也包括幾位來自歐洲、南美洲、北美洲、亞洲和非洲等國際學術期刊的主要編輯，他們對我們的期刊和論文都給予肯定，也希望 INFORMS 的期刊可以與我們的期刊作更多的互動，給我們很多的建議。

林蔚君博士在會後也邀請國際期刊的編輯和部份 INFORMS 國際部的成員開會討論增加互動的具體作法，希望能為新進人員和博士生製造更多的曝光機會。

因為臺灣已經成立 INFORMS Taiwan chapter，我和王逸琳教授參加 Chapters 的早餐會，我們代表臺灣和其他的成員交換工作經驗，也為國際人士介紹臺灣相關的學術以及學生活動。

二、與會心得

這次報告的論文是 102 年度執行計畫的部份結果，雖然在場的人不都是研究等候模型的，但是也提供許多建議，為未來研究增加議題性和發展性。

三、發表論文全文或摘要

Title: Computing the Waiting Time in a Security Check System

Abstract: The objective of this presentation is to introduce a queueing model to assist the Transportation Security Office understand how to design and manage the security wait environment with customers' satisfaction, for example the normal wait time is no more than 30 minutes. To meet the security conditions in practice, such as checks in various security stages, we use a queueing model with service time of semi-Coxian distributions. The semi-Coxian distribution in fact complicates the computation but reflects relatively better estimation than a traditional model. Thus, it is useful both to maintain the security level and to release the tense in the security check points in airports, or international borders.

四、建議

INFORMS 的學術活動是值得向國人介紹和推廣的。

五、攜回資料名稱及內容

大會議程和 1600 多篇的論文摘要電子檔。

六、其他

無。

國立政治大學發展國際一流大學及頂尖研究中心計畫
出國成果報告書（格式）

計畫編號[1]		執行單位[2]	理學院
出國人員	陸行	出國日期	104 年 8 月 25 日至 104 年 9 月 15 日，共 21 日
出國地點[3]	馬來西亞吉隆坡	出國經費[4]	

報告內容摘要(請以 200 字～300 字說明)

目的：

國際合作和訪問的對象是 Monash University Malaysia 的 Dr. Kenneth Lee 和 Dr. David Wu。他們協助我進行科技部研究計畫與開發模擬計算模式和比較模擬結果。因為他們對於亞洲人與馬來西亞人在使用藥物和經濟成本效益之特質和分析的經驗，以及比較了解相關文獻與資料。我向他們學習後，開發 TreeAge 的模擬程式，如後頁所示。同時配合政大理學院的發展，介紹政大的師生在學術研究和學習方面的情形。

過程：

於移地研究期間我特別拜訪幾位有興趣與臺灣合作的老師，名單如下。彼此一致的想法是，合作案必須持續推動。

- Professor Dr. Pervaiz Ahmed, Deputy Head of School and Director of Research, School of Business，會談時間在 2015-08-28（週五）下午 2 點。另附相片於後頁。
- Prof Daniel Reidpath (Global Public Health) ，會談時間在 2015-09-03（週四）下午 2 點。
- Dr. Kuang Ye Chow, Associate Head of School (Research Training) School of Engineering，會談時間在 2015-09-08（週二）下午 2 點。
- Dr. Wong Chee Piau, Associate Professor, Jeffrey Cheah School of Medicine and Health Sciences，會談時間在 2015-09-09（週三）下午 12 點。

另外也擔任在職班 Dr. M Hafeezul Suraj A Wilson 的論文口試委員，時間在 2015-09-11（週五）下午 2 點。而且於 2015-08-27（週四）下午 2 點擔任論文專題演講人；於 2015-09-10（週四)擔任模擬課程工作坊主講人。也和下列幾位主要學術行政負責人討論合作事宜。

---

[1] 單位出國案如有 1 案以上，計畫編號請以頂大計畫辦公室核給之單位計畫編號 +「-XX（單位自編 2 位出國案序號）」型式為之。如僅有 1 案，則以頂大計畫單位編號為之即可。

[2] 執行單位係指頂大計畫單位編號對應之單位。

[3] 出國地點請寫前往之國家之大學、機關組織或會議名稱。

[4] 出國經費指的是實際核銷金額，單位以元計。

- Professor Dr. Iekhsan Othman, Jeffrey Cheah School of Medicine and Health Sciences
- Prof. Kenneth Lee, Dr. David Wu, Dr. Tahir Mehmood Khan, Dr. Shaun Lee, Department of Clinical Pharmacy.

心得及建議事項：

因為這個研究工作牽涉數學模式與理論、工程程式與工具開發撰寫、公共經濟與衛生專家、統計學家和臨牀專業醫生等不同背景的知識，本人是一邊學一邊做。同時感謝不同領域專家的協助，讓計畫得以進行。

未來，這個模式仍要繼續開發，同時也透過政大，希望建立與 Monash University Malaysia 的合作互訪機制，持續努力完成離散事件模擬法在藥物經濟成本效益分析的決策支援系統模型。馬來西亞方面對於和台灣的交流表示強烈的意願。本人僅獻棉薄之力。除了進行國民外交，與 Monash University 學者產生良好的互動，互相交換研究心得，增加彼此了解，加強友誼，對於未來的研究工作和國際交流有正面而且直接的影響。

建議事項參採情形[5]	出國人建議		單位主管覆核		
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2.					
3.					

出國人簽名：　　日期：

連絡人：　　分機：

[5]出國參加學術會議、發表論文者，此欄位可不必填寫。

出國報告審核表

<table>
<tr><td colspan="4">出國報告名稱：　　科技部研究計畫移地研究暨拜訪會商理際合作之出國報告</td></tr>
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<tr><td>計畫主辦機關審核意見</td><td colspan="3">☐1.依限繳交出國報告
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☐於本機關業務會報提出報告
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一、 各機關可依需要自行增列審核項目內容，出國報告審核完畢本表請自行保存。

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附件

HBV Infection Prognosis Prolonged Simulation Models

ABSTRACT

Objectives: Chronic hepatitis B virus (HBV) infection is a dynamic process with an early replication phase and active liver disease. HBV can result in long-term infection causing a serious clinical problem, affecting 350-370 million individuals worldwide. Several unresolved issues are difficult to address using currently available clinical data. These include prognosis of hepatitis B with its natural history and the relative cost-effectiveness of the management procedures. Markov models and decision trees are commonly used in disease progression simulation. However, these methods cannot reflect the clinical appearance more flexibly and alternatively. Therefore, this requirement develops a discrete-event computer simulation model for the analysis of HBV disease progression. Discrete Event Simulation (DES) presents a flexible and powerful analysis tool for respective purposes in HBV studies. In this paper, we developed a DES model based on the natural course of HBV infection. The celebrated Gompertz function and the life table are applied the developed model. The model is effective by resembling individuals or cohorts of hypothetical patients while tracking disease progression and survival.

Methods: We consider that the disease progression is originally described by a Markov model, and propose a new method to approximate the HBV progression with clinical data. Instead of the additive assumption, this resulting model is established based on conditional probabilities and a life table.

Results: For a patient at age 25, the expected remaining life expectancy, and the maximal life year for him or she is 36.31 years and 80 years respectively. This patient has 16.37% probability of death/transplantation within 20 years because of HBV infection or population mortality.

Conclusion: Numerical results show that the proposed model can be applied to obtain a more realistic life expectancy, the survival probabilities at various initial ages, and mortalities from various initial symptoms to death. Meanwhile, its applications to derive the probabilities for patients' first experiencing critical medical status during a specified duration and its generalization to include multiple transition related factors are discussed.

Keywords: Markov chain, disease progression, life table, first passage time, survival probability.

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1. Introduction

Simulation in healthcare as an academic subject has been widely explored and well doucmented. During the past decades, simulation modeling in healthcare has been referred to wide range of

applications from health risk assesssment, cost-benefit analysis and policy evaluation of medical treatment, diesase menagement, planning of healthcare services, training and healthcare decision support system, etc. [15], Computer simulation is a technique of informatics which allows stake holder to conduct experiments with model and ideally provides a communication platform in healthcare for administratiors and clinicians to to find better solutions for patients or tax payers.

Chronic hepatitis B virus (HBV) infection is a dynamic process with an early replication phase and active liver disease. HBV can result in long-term infection causing a serious clinical problem, affecting 350-370 million individuals worldwide. Disease progression modeling is generally recognized as a practical framework in considering related medical applications. Chronic hepatitis B inflicts an almost incredulous toll on the planet, affecting greater than 400 million people [11]. In Taiwan, chronic hepatitis B virus (HBV) infection and its potential adverse sequel are major causes of morbidity, mortality and medical expenditure. Chronic liver disease was the sixth leading cause of death in 2000 and hepatocellular carcinoma (HCC) was the most common cancer in 1997 [21]. According to Liver Disease Prevention & Treatment Research Foundation, there are 3 million people has been affected at a cost of more than US$ 3 million annually in Taiwan. Markov models and decision trees are most commonly used in disease progression simulation.

However, Markov models and decision trees are less able to reflect the clinical appearance more flexibly and alternatively. The risk of disease progression depends on the characteristics of the patients [3]. These models should take age, sex, disease severity, blood type, economical ability, and environmental factors into account simultaneously. Moreover, decisions about when a patient should take more aggressive medicine or when to have an operation are based not only on symptoms but also on social and environmental factors. Variables should be defined to contain factors that change over time to reflect the disease more naturally. Outcomes are costs, disease episodes and symptoms. Sensitivity analyses about cost or transition probabilities should be contained as well [4].

Therefore, this kind of requirement develops a discrete-event computer simulation model for the analysis of HBV disease progression. This paper describes the development of a model to assess the dependencies between a broad range of parameters in the treatment of disease. Discrete-event computer simulation has been widely used inside the management science and operations research contexts since it is already known as an important design tool for versatile applications. Importantly, this kind of simulation has been shown to be a fast and low-cost approach for health management modeling [2, 4]. The individual experience is modeled over time in terms of the events that occur and the consequences of those events. This approach is superior to the traditional Markov models. [3].

DES proceeds very efficiently because the clock is successively advanced to the time when the next event will occur, without wasting effort in unnecessary interim computations [2]. In other words, time advances in ‘discrete’ jumps. By making time explicit, a DES avoids one of the major problems of decision trees [2]. It also enables handling of time that is much more flexible than in Markov models

since there is no need to declare a cycle length. Although cohort Markov models may involve fewer calculations, they require gross oversimplifications making them rarely suitable for informing real decisions.

2. Natural History

Chronic HBV infection is a dynamic process with an early replicative phase and active liver disease and a late low or nonreplicative phase with remission of liver disease. Persistence of HBsAg, hepatitis B e antigen (HBeAg) and HBV-DNA in high titer for more than 6 months implies progression to chronic HBV infection [1]. The variability in chronic hepatitis B has led to its classification into phases of disease based upon alanine aminotransferase (ALT) elevations, the presence of HBeAg, HBV-DNA levels and suspected immune status. The duration of typical HBeAg-positive chronic hepatitis B can be prolonged and severe and may result in cirrhosis [7,16].

Immune tolerance phase:

The presence of circulating HBsAg, HBeAg and high levels of serum HBV-DNA identifies the first immunotolerant phase. Perinatally acquired HBV infection is characterized by a prolonged "immunotolerant" phase with HBeAg positivity, high levels of serum HBV-DNA, normal levels of aminotransferases, minimal liver damage and very low rates of spontaneous HBeAg clearance. A proportion of HBeAg-positive persons, have no ALT elevations and scant histological activity. In Asia, it is most common in children, adolescent, and young adults [11].

Immune clearance phase:

The second immunoactive phase which is associated with a decrease in HBV-DNA concentrations and increased ALT levels and histological activity reflects the host immune mediated lysis of infected hepatocytes [7]. Patients with childhood or adult acquired infection and chronic hepatitis B usually present in the "immunoactive" phase with elevated aminotransferases and liver necroinflammation at histology and approximately 50% will clear HBeAg within 5 years. This phase marks the incubation period of acute HBV infection and lasts about two to four weeks, in contrast with perinatal infection this phase often lasts for decades in which patients with chronic HBV infection has a variable duration from months to years [11]. Hepatitis flares during treatment were defined as elevations in the alanine aminotransferase level to more than twice the baseline level and to more than 10 times the upper limit of normal [13].

Residual phase is the third low or non-replicative phase involves seroconversion from HBeAg to antibody to HBeAg (anti-HBe) usually preceeded by a marked reduction of serum HBV-DNA levels below 105 copies per ml, that are not detecTable Ay hybridization techniques, and followed by normalization of ALT levels and resolution of liver necroinflammation. Serum HBV-DNA remains detectable only by ultrasensitive technique of polymerase chain reaction (PCR) in many patients. In chronic HBV infection this phase is also referred as the inactive HBsAg carrier state. The inactive chronic HBV infection may last for lifetime, but a proportion of patients may undergo subsequent

spontaneous or immunosuppression induced reactivation of HBV replication with reappearance of high levels of HBV-DNA with or without HBeAg seroreversion and rise in ALT levels [11, 16].

HBV can be classified into 7 genotypes A-G and recent studies, all from Asia, have indicated that HBV genotype B is associated with earlier HBeAg seroconversion than genotype C, thus most likely explaining the less progressive disease in patients with genotype B [6, 8, 19]. HBeAg seroconversion associated with liver disease remission marks the transition from chronic hepatitis B to the inactive HBsAg carrier state, however a small percentage of patients (approximately 5%) may continue to show biochemical activity and high levels of serum HBV-DNA at the time of HBeAg seroconversion [1, 12, 14]. These patients as well those undergoing reactivation of hepatitis B after HBeAg seroconversion may generate the group of patients with HBeAg negative chronic hepatitis B.

Figure 1 presents a model with a slight modification by Liaw and Chu [27]. Here we take numerical experiments based on Figure 1 by some required approximations and modifications stated in the following. First, we assume that several estimates in Figure 1 are annual transition probabilities rather than percentages. Second, the state "curative therapy" is combined with the state "death/transplantation." and replaced with the state "death". Besides, no treatments are applied to patients. Third, in Figure 1, the annual transition probability from "HBeAg(+) hepatitis HBV-DNA> $2\times10^{6\sim7}$ IU/ml" to "HBeAg(+) hepatitis HBV-DNA> $2\times10^{4\sim5}$ IU/ml" and "HBeAg seroconversion" is assumed to be 15% per year.

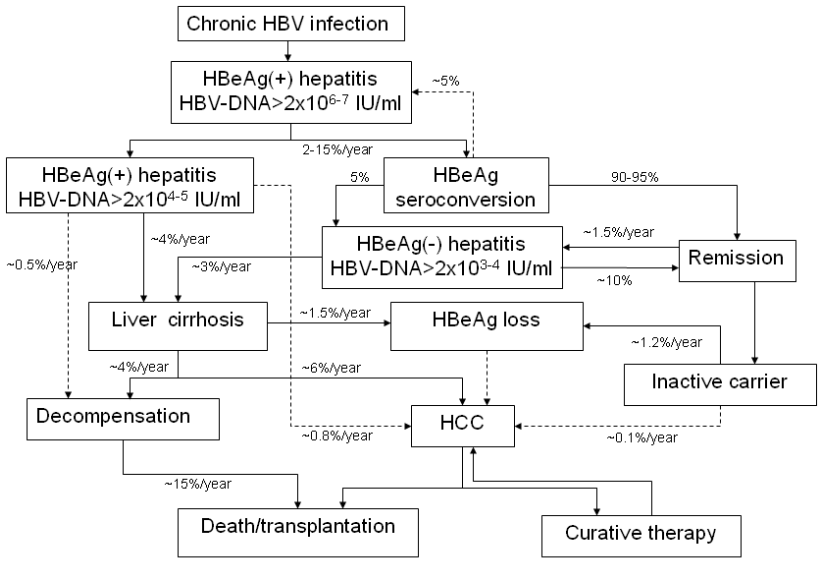

Figure 1: A transition diagram of chronic HBV progression from Liaw and Chu [27].

The outward annual transition probability from state "HBeAg(+) hepatitis HBV-DNA> $2\times10^{6\sim7}$ IU/ml" is assumed to be 15% per year. We may assume that the ratio between transitions to "HBeAg(+) hepatitis HBV-DNA> $2\times10^{4\sim5}$ IU/ml" and transitions to "HBeAg seroconversion" is approximately 2:1. In other words, annual transition probability to "HBeAg(+) hepatitis HBV-DNA> $2\times10^{4\sim5}$ IU/ml" is

10% per year and annual transition probability to “HBeAg seroconversion” is 5% per year. Figure 2 summarizes the modifications.

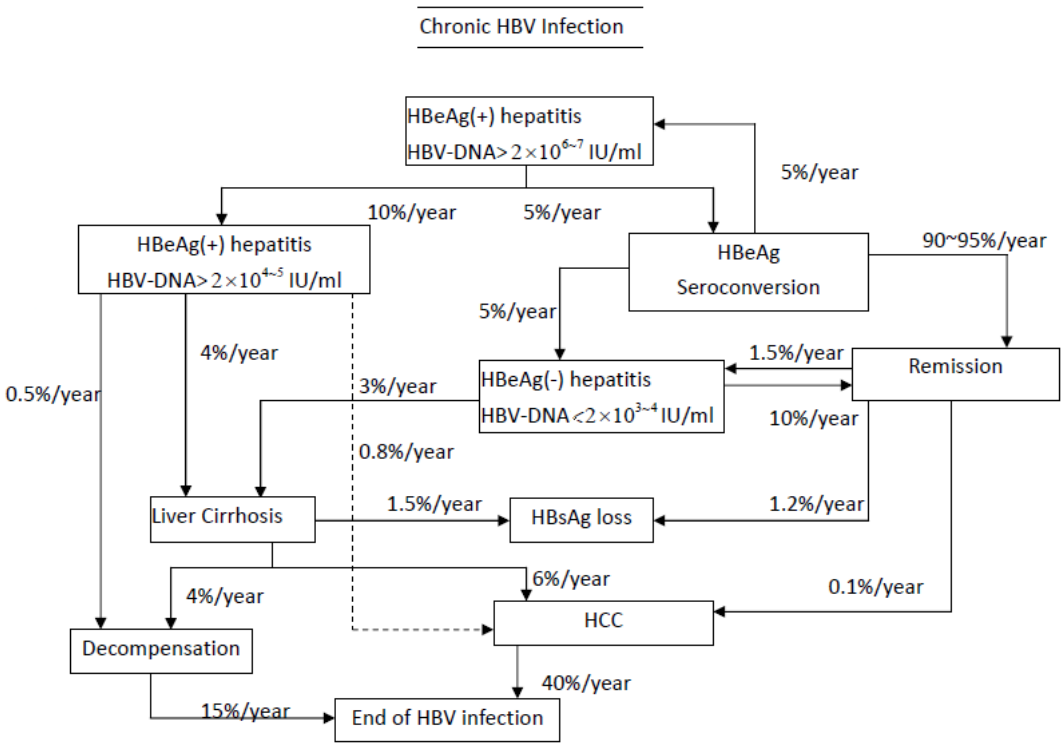

Figure 2: The modified transition diagram of Chronic HBV progression.

In Figure 2, consider a random variable sequence $X=\{X_n, n\in \mathrm{N}\}$ and $T=\{T_n, n\in \mathrm{N}\}$ defined on a probability space (Ω, F, P) with a finite set $E=\{s_1, s_{2,}, \cdots, s_m\}$, $m\in \mathrm{N}$, where N is the set of all positive integers. For example, s_1 denotes the health status of HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL; s_2 denotes the health status of HBeAg(-) hepatitis HBD-DNA> $2\times10^{3\sim4}$ IU/mL, and so on. X_n represents the state at the n^{th} transition and T_n denotes the time before the n^{th} transition. If $X_n=i$ and $i\in E$, then the process is said to be in state i at time n. For any nonnegative integer n and any state $i, j, i_0, \cdots, i_{n-1}$, we have:

$$p_{i,j}=P(X_{n+1}=j \mid X_0=i_0, X_1=i_1, \cdots, X_{n-1}=i_{n-1}, X_n=i)=P(X_{n+1}=j \mid X_n=i).$$

In addition, if state j is not adjacent to state i in the HBV disease progression model, then the probability $p_{i,j}$ is assumed to be 0. We define

$$p_i=\sum_{j=1}^{m} p_{i,j},$$

where p_i denotes the probability for a patient to leave state i in one year.

3. Gompertz Distributions

The principal focus of the analysis was to determine the relative transitions of hepatic liver disease in patients with clinical symptoms. An analysis with best estimates for all model parameters and event probabilities was carried out from a societal perspective following the consensus recommendations of

Liaw and Chu [27]. Instead of the conventional Markov Model in most published papers on such outcome studies, the methodology is to use discrete event simulation for prognosis of HBV modeling. The model tracks the liver disease status, virus activity, clinical symptoms, and age of each patient. Survival life is predicted on the basis of disease extent.

The celebrated Gompertz distribution [18] is introduced in the DES model. We assume that each state i follows the Gompertz distribution with different parameters a_i and b_i. The probability density function of Gompertz distribution is given as

$$f_i(t;\ a_i,\ b_i) = b_i \cdot e^{a_i t} \exp[\frac{b_i}{a_i}(1-e^{a_i t})]$$

for $0 < t < \infty$, $a_i > 0$, and $b_i > 0$ (0 otherwise). The corresponding cumulative distribution function is

$$F_i(t;\ a_i,\ b_i) = 1-\exp[\frac{b_i}{a_i}(1-e^{a_i t})].$$

In every state, it is essential to estimate the time interval of such a health state in simulation. Denoting by T the time interval of a specific state i, the probability of an incidence occurrence before time t where $T \le t$ is

$$P(T_{n+1}-T_n \le t|\mathrm{X}_n = i,\ X_{n+1} \ne i) = F_i(t;\ a_i,\ b_i) = 1-\exp[\frac{b_i}{a_i}(1-e^{a_i t})]. .$$

In particular, for every state i, the probability of an incidence occurrence within one year is $T \le 1$. Hence, we have

$$P(T_{n+1}-T_n \le 1|\mathrm{X}_n = i,\ X_{n+1} \ne i)) = 1-\exp[\frac{b_i}{a_i}(1-e^{a_i})] = p_i.$$

For given transition probability p_i and a_i in state i, we have b_i as a function of a_i written as

$$b_i = f(a_i) = \frac{a_i \ln(1-p_i)}{1-e^{a_i}}.$$

In DES, the average length of time intervals of the nonabsorbing state is estimated by $1/p_i$. For each simulation run, we converted all available data into annual probability estimates for use in the DES model. We calculated these annual estimates of each time period that a state will experience. Hence, we know that

$$P(T_{n+1}-T_n \le t|\mathrm{X}_n = i,\ X_{n+1} \ne i) = F_i(t;\ a_i) = 1-\exp[\frac{\ln(1-p_i)}{1-e^{a_i}}(1-e^{a_i t})].$$

According to Yousef [18], the mean $u_t|_i$ of the distribution is

$$u_t|_i = \frac{1}{a_i} e^{\frac{b_i}{a_i}} \left[\ln a_i - \ln b_i - \gamma - \sum_{k=1}^{\infty} \frac{\left(-\frac{b_i}{a_i}\right)^k}{k \cdot k!} \right],$$

where $\gamma \sim 0.5772$ is an Euler's constant. Hence, the equation of $u_t|_i$ for each status can be rewritten as

$$u_t\,|_i = \frac{1}{a_i} e^{\frac{\ln(1-p_i)}{1-e^{a_i}}} \left[\ln \frac{1-e^{a_i}}{\ln(1-p_i)} - \gamma - \sum_{k=1}^{\infty} \frac{\left(-\frac{\ln(1-p_i)}{1-e^{a_i}} \right)^k}{k \cdot k!} \right].$$

We want to choose proper a_i for each state to fit that $u_t\,|_i \approx 1/p_i$, so we solve the equation $u_t\,|_i - 1/p_i = 0$ for a_i for different status. Table 1 summarizes the results of a_i and b_i. Note that the status "Death/Transplantation" is the absorbing state. In addition, for the state "HBeAg seroconversion", every patient in this symptom is assumed to stay for one year and then transfers to another states. For patients at "HBsAg loss", he will follows the population mortality instead of the Gompertz distribution.

Table 1: The symbols and parameters a_i and b_i of states in Figure 2.

Symptoms	State symbol	a_i	b_i
HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL	s_1	0.11	0.0004
HBeAg(+) hepatitis HBD-DNA> $2\times10^{4\sim5}$ IU/mL	s_2	0.4	0.0001
HBeAg seroconversion	s_3	None	None
HBeAg(-) hepatitis HBD-DNA< $2\times10^{3\sim4}$ IU/mL	s_4	0.095	0.0004
Remission	s_5	0.02	0.0001
Liver cirrhosis	s_6	0.081	0.0003
HBsAg loss	s_7	None	None
Decompensation	s_8	0.11	0.0004
HCC	s_9	0.28	0.0011
Death/Transplantation	s_{10}	None	None

4. Model Overview

To articulate the natural course of chronic HBV, a discrete-event simulation model was developed with the ProModel [20]. This model is based on the concepts of entities, locations, processes, time of events and attributes. In this study, an entity represents a patient in the disease progression. Locations are liver status where the processes are the routines that connect locations. Processes will decide how an entity will work in every location, where the Gompertz distribution [18] and the life table [22] are embedded. Attributes are the possible clinical symptoms of patients which are presented by entities. These elements, taken together with discrete time of every possible events of a system, allow for the construction of computer models that represent the system actual operating conditions. Basic system parameters are excerpted from the literature given in Liaw and Chu [27], and the life table [22] is described in Appendix.

We developed a Discrete Event Simulation model based on the natural course of Chronic HBV [9, 16, 27]. In this section, the proposed DES model will be expounded in detail. Flow diagram of the computation process for a discrete event simulation is also discussed. The life table [22] is also concluded in the DES model, which is given in Appendix.

4.1 Entities

A central component of DES is the entity which denotes the patient in modeling. In contrast to decision trees and Markov models, which do not specify the patient but instead focus exclusively on outcomes or states, the patient is an explicit element in a DES. A DES model allows introducing interactions between patients or different status while a Markov Monte-Carlo microsimulation deals with one health status at a time. It is important while modeling for infectious diseases.

Patients have attributes of which individual has a specific value for each characteristic. These values are defined at the start of the simulation and updated at particular points in time. Two important attributes of patients are the time to reach the significant status and the sojourn time in status. When patients start infected with HBV, they are concerned about how much time they have to reach the worse status, how much time they could stay healthy, what the remaining life expectancy is for them, or what the survival probability is in the future. Attributes in DES play an important part in estimating.

4.2 Locations

The model contains ten liver statuses as in Table 1: HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL, HBeAg(+) hepatitis HBD-DNA> $2\times10^{4\sim5}$ IU/mL, HBeAg seroconversion, HBeAg(-) hepatitis HBD-DNA> $2\times10^{3\sim4}$ IU/mL, remission, liver cirrhosis, HBsAg loss, decompensation, hepatocellular carcinoma, and death/transplantation. Each liver status is defined as a location in this model. All patients begin in the Chronic HBV infection and enter HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL immediately. Patients change to any of the liver statuses with given probability according the Gompertz function. When entities entered a location, they will follow the rule of processing defined on each location to decide how long they would stay in this location and where to go for the next. A demonstration of DES model is shown as Figure 3.

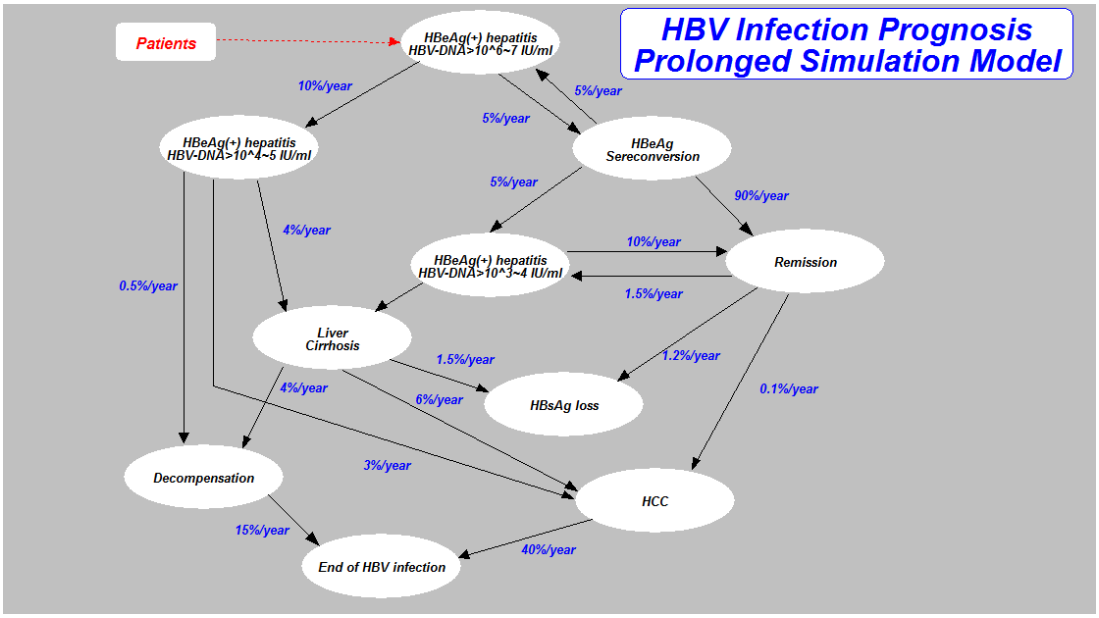

Figure 3: A demonstration of DES model

4.3 Processing

Processing guides how an entity acts in a location. Figure 4 shows how a patient will move in this DES disease progression. First, a HBV patient is created and then he starts his own HBV disease progression. Generally speaking, an entity will reach the status "HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL". Then the entity will decide how long he will stay at the state "HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL" according to the Gompertz function given in Section 5. For a entity at this status, given a random number $0 \le r \le 1$, we have the waiting time T_1 for this patient at this state by

$$T_1 = \frac{1}{a_1}\ln(\ln\frac{e}{(1-r)^{1-e^{a_1}/\ln(1-p_1)}}).$$

That is, this patient will spend time T_1 at current state. After waiting time T_1 in the state "HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL" for a while, the entity will decide whether he will die or not according to the population mortality or disease progression. If the entity died, then he simply reaches the final status "Death". If the entity does not die, he will leave the current state and reach another state s_j, $j \sim i$. Then the entity repeats the progression rule for another state s_j again until he reaches the final state "Death".

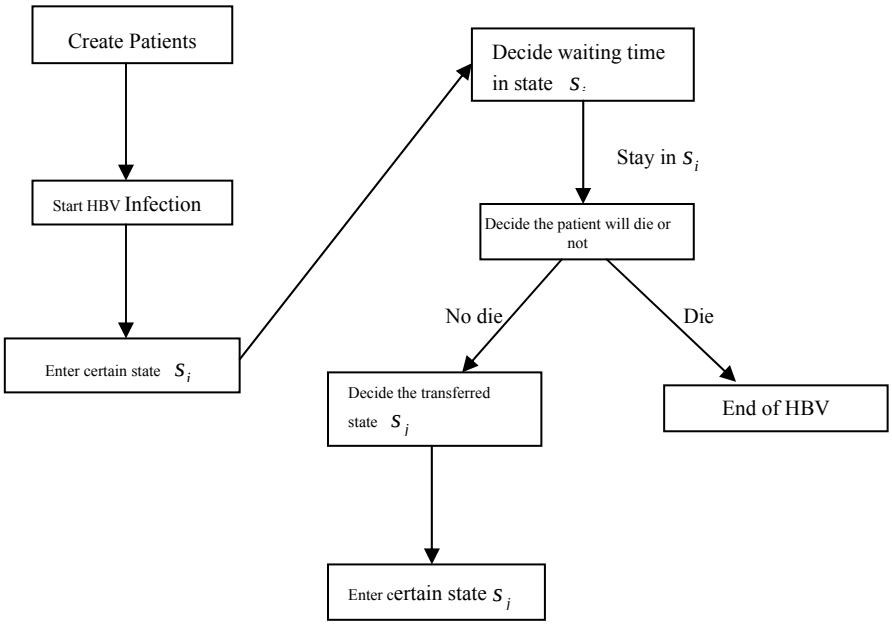

Figure 4: The flow chart of the DES disease progression.

5. The Outcome of DES Model

5.1 The outcome of DES model

This process continues until a predetermined time is reached, at which point the simulation is terminated. The basic model includes only a generic setting and no treatment strategy. The model is effective by simulating cohorts of hypothetical patients while tracking disease progression, complications, and survival. For each set of model assumptions under consideration, we may simulate hypothetical cohorts of patients.

The model tracks up to 10 individual hepatic clinical symptoms in each patient, specifying and updating liver disease status shown in Table 1. Percentages of occurrences at different liver status are given in Figure 2. For each hypothetical patient, the type of virus activity is chosen at random from a population distribution conditioned on a previous liver status and other variables. The type of virus activity is then distributed throughout the simulation. We assume that each patient has an independent, equal probability of being infected by virus**.** The clinical symptom of each patient is similarly selected at random from a population distribution but mainly depending on the previous condition. We assume time advances with Gompertz distributions and that no new liver disease develops between any two occurrences, since all events are assumed to happen at discrete time manner. Events can happen in any logical sequence and even simultaneously. They can recur if that happens in reality and they can change the course of a given patient's experience by influencing that patient's attributes and the occurrence of future events with no restriction on 'memory'.

In the DES, the model is assumed to have a lifetime horizon and a cycle length of 75 years with patients with HBV at age 25. In ProModel, one year is assumed to be 360 days, so we setup the time limit to be $75 \times 360 = 27000$ days. Note that the unit of the results is days. The simulation is repeated for 10 times, and in every simulation 20000 patients are involved. The simulated results are shown in Figure 5.

Variable Name	Total Changes	Average Hours Per Change	Minimum Value	Maximum Value	Current Value	Average Value	
remission time*	8880.6	3.03	0.69	25919.5	13776.6	4831.26	(Average)
remission time*	129.30	0.04	0.84	313.71	4938.26	90.49	(Std. Dev.)
e loss time*	6784.1	2.15	365	365	365	365	(Average)
e loss time*	71.86	0.34	0	0	0	0	(Std. Dev.)
decompensation time*	4942	5.42	0.45	10934.9	3806.35	2400.5	(Average)
decompensation time*	86.77	0.09	0.32	12.61	2715.02	24.00	(Std. Dev.)
cirrhosis time*	10924	2.46	0.21	10942.6	2108.21	2754.7	(Average)
cirrhosis time*	99.49	0.02	0.22	5.28	1137.31	22.45	(Std. Dev.)
DNA1034 time*	4628.4	5.82	0.75	10937.3	3256.45	2604.57	(Average)
DNA1034 time*	114.03	0.14	0.46	11.36	2957.59	26.53	(Std. Dev.)
DNA1045 time*	13441.5	1.65	0.19	10945.7	9643.12	3966	(Average)
DNA1045 time*	72.97	0.08	0.18	3.66	807.24	22.76	(Std. Dev.)
HCC time*	7789.7	3.44	0.48	10936.9	2530.07	2162.96	(Average)
HCC time*	58.67	0.03	0.39	11.49	4026.27	24.65	(Std. Dev.)
sloss time*	4661.4	5.79	365	25258	18469	11424.7	(Average)
sloss time*	86.69	0.10	0	335.41	3025.56	91.99	(Std. Dev.)
DNA1067 time*	20337.4	0.76	0.08	10838.5	9350.77	1979.67	(Average)
DNA1067 time*	12.60	0.11	0.07	90.59	1381.96	6.92	(Std. Dev.)
time 2 DNA1045*	13441.5	1.65	2.85	15246.5	12667.8	2023.43	(Average)
time 2 DNA1045*	72.97	0.08	0.09	1695.3	1397.07	11.31	(Std. Dev.)
time 2 DNA1034*	4628.4	5.82	376.98	26266.4	14561	6648.72	(Average)
time 2 DNA1034*	114.03	0.14	6.22	436.95	10504.6	90.68	(Std. Dev.)
time 2 DNA1067*	20337.4	0.76	1	1	1	1	(Average)
time 2 DNA1067*	12.60	0.11	0	0	0	0	(Std. Dev.)
time 2 HCC*	7789.7	3.44	165.99	26318.9	24307.3	8268.19	(Average)
time 2 HCC*	58.67	0.03	76.35	368.78	4071.7	33.37	(Std. Dev.)
time 2 decompensation*	4942	5.42	253.8	25383.3	22995.2	8259.16	(Average)
time 2 decompensation*	86.77	0.09	93.94	583.24	2868.77	74.37	(Std. Dev.)
time 2 cirrhosis*	10924	2.46	61.96	25639.1	24771.3	6379.1	(Average)
time 2 cirrhosis*	99.49	0.02	34.14	650.03	1101.41	38.73	(Std. Dev.)
time 2 eloss*	6784.1	2.15	3.03	7661.08	3004.72	1951.19	(Average)
time 2 eloss*	71.86	0.34	0.23	383.03	755.08	18.34	(Std. Dev.)
time 2 sloss*	153932	0.17	472.56	26592.2	9441.76	7331.55	(Average)
time 2 sloss*	2985.81	0.00	125.83	34.23	4471.74	50.30	(Std. Dev.)
time 2 remission*	8880.6	3.03	369.12	14833.5	1934.34	2504.89	(Average)
time 2 remission*	129.30	0.04	0.24	736.14	1009.92	21.98	(Std. Dev.)
time to death*	19134.3	1.41	21.21	26995.4	26995.4	13070.5	(Average)
time to death*	24.59	0.00	12.68	4.18	4.18	53.37	(Std. Dev.)

Figure 5: The results of the HBV disease progression model.

From Figure 5, there are the results of the HBV disease progression model. The results are classified into 2 parts. Take the status "remission" for example, one is the word "remission time", and the other is "time 2 remission". "Remission time" represents the time a patient spent in status remission, whereas "time 2 remission" means the time a patient spent before reaching the status "remission" for the first time. The time unit in Figure As the titles in Figure 5, we focus on the average value. The average value for "remission time" is 4831.26 days, and 90.49 days is the standard deviation for the results. The average value for "Time 2 remission" is 2504.89 days with standard deviation 21.98 days. In other words, the average value for "remission time" and "Time 2 remission" is 4831.26/360=13.42 years and 2504.89/360=6.96 years respectively. Table 2 summarized the results of Figure 5. Note that the time unit in Figure 5 is days, and the time unit in Table 2 is years.

Table 2: The average sojourn time in different liver status and the average time to reach different liver status in Figure 2

Symptoms	The average sojourn time	The average time
HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL	5.50 years	None
HBeAg(+) hepatitis HBD-DNA> $2\times10^{4\sim5}$ IU/mL	11.02 years	5.62 years
HBeAg seroconversion	1 year	5.42 years

HBeAg(-) hepatitis HBD-DNA> $2\times10^{3\sim4}$ IU/mL	7.23 years	18.46 years
Remission	13.42 years	6.96 years
Liver cirrhosis	7.65 years	17.72 years
HBsAg loss	31.74 years	20.37 years
Decompensation	6.67 years	22.94 years
HCC	6.01 years	22.97 years
Death	None	36.31 years

This model was constructed by a systematic search of the literature to identify source materials on the natural history, epidemiology of HBV, and demography. In the state transition model, patients with HBV may remain in that state, move on to more progressive stages of liver disease or may clear the disease. The model has a lifetime horizon and a cycle length of 75 years, assuming a patient with HBV at age 25. Table 2 demonstrates the average sojourn time in each liver status and the average time for a patient at age 25 to reach different liver status. The patients are estimated to wait 7.65 years at the liver status liver cirrhosis and 31.74 years at HBsAg loss respectively. Moreover, it is approximated about 17.72 years for a patient at age 25 to reach the liver status liver cirrhosis. The remaining life expectancy is predicted about 36.31 years for a patient at age 25 at the beginning of HBV infection. The outcomes analysis of our study presents a byproduct of the development of DES, which illustrates the usage of DES.

5.2 DES versus Markov

In this section, we compare the results of a DES model and a Markov model for chronic HBV disease progression. The results are based on assuming that the patients are at state s_1 starting at age 25. Table 3 represents the outcome of a DES model and Table 4 shows the result of a Markov model.

Table 3: The simulated disease progression probabilities distribution for a DES model

States / Ages	s_1	s_2	s_3	s_4	s_5	s_6	s_7	s_8	s_9	s_{10}
25	1	0	0	0	0	0	0	0	0	0
30	0.4864	0.3059	0.0308	0.0130	0.1104	0.0306	0.0061	0.0044	0.0072	0.0054
35	0.1452	0.4126	0.0177	0.0367	0.1814	0.1028	0.0308	0.0200	0.0312	0.0221
40	0.1448	0.4126	0.0177	0.0367	0.1814	0.1030	0.0308	0.0196	0.0312	0.0221
45	0.0065	0.2146	0.0007	0.0623	0.1273	0.1667	0.1137	0.0570	0.0877	0.1637
50	0.0036	0.1202	0.0006	0.0540	0.0931	0.1426	0.1534	0.0590	0.0872	0.2872
55	0.0005	0.0135	0.0002	0.0340	0.0425	0.0699	0.2054	0.0410	0.0562	0.5370
60	0.0001	0.0023	0	0.0231	0.0327	0.0381	0.2094	0.0273	0.0349	0.6320
65	0	0.0007	0	0.0148	0.0266	0.0181	0.2014	0.0159	0.0187	0.7039
70	0	0.0003	0	0.0091	0.0221	0.0093	0.1814	0.0094	0.0091	0.7593
75	0	0.0002	0	0.0056	0.0188	0.0047	0.1497	0.0049	0.0040	0.8122
80	0	0.0001	0	0.0040	0.0141	0.0023	0.1101	0.0025	0.0019	0.8659

Table 4: The simulated disease progression probabilities distribution for a Markov model

States / Ages	s_1	s_2	s_3	s_4	s_5	s_6	s_7	s_8	s_9	s_{10}
25	1	0	0	0	0	0	0	0	0	0
30	0.4479	0.3275	0.0263	0.0096	0.1379	0.0289	0.0034	0.0047	0.006	0.0078
35	0.201	0.3948	0.0118	0.0185	0.2075	0.076	0.0173	0.0166	0.0158	0.0407
40	0.09	0.3639	0.0053	0.0233	0.225	0.1044	0.0367	0.0279	0.0218	0.1017
45	0.0401	0.3031	0.0024	0.0251	0.2206	0.1122	0.0578	0.0345	0.0234	0.1808
50	0.0178	0.2399	0.001	0.0249	0.2072	0.106	0.0778	0.0363	0.0222	0.2669
55	0.0078	0.1841	0.0005	0.0237	0.1901	0.0926	0.0952	0.0343	0.0194	0.3524
60	0.0034	0.1375	0.0002	0.0217	0.1707	0.0763	0.1086	0.0299	0.016	0.4358
65	0.0015	0.1	0.0001	0.0193	0.15	0.0599	0.1171	0.0245	0.0126	0.5151
70	0.0006	0.07	0	0.0164	0.1272	0.0447	0.1187	0.0189	0.0094	0.5941
75	0.0002	0.0463	0	0.0133	0.1022	0.0312	0.1119	0.0134	0.0066	0.6748
80	0.0001	0.0282	0	0.0098	0.0755	0.0199	0.0955	0.0087	0.0042	0.7582

Table 3 and Table 4 show the simulated disease progression probabilities distribution. After ten years, about 14.52% it will be in s_1 and 18.14% in s_5, and 2.2% in s_{10} in a DES model, whiles about 9% it will be in s_1 and 20.75% in s_5, and 4% in s_{10} in a Markov model. Likewise, the other probabilities can be interpreted in the same manner. Figure 6 and Figure 7 show the corresponding survival probability simulated from a DES and a Markov model respectively. Moreover, the remaining life expectancy for DES model and Markov model are 36.31 years and 39.48 years.

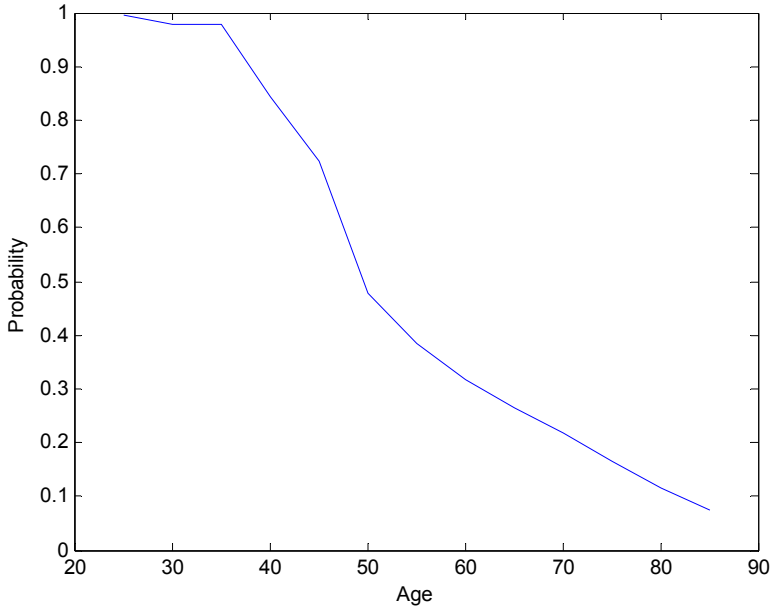

Figure 6: The survival probability of different ages starting at age 25

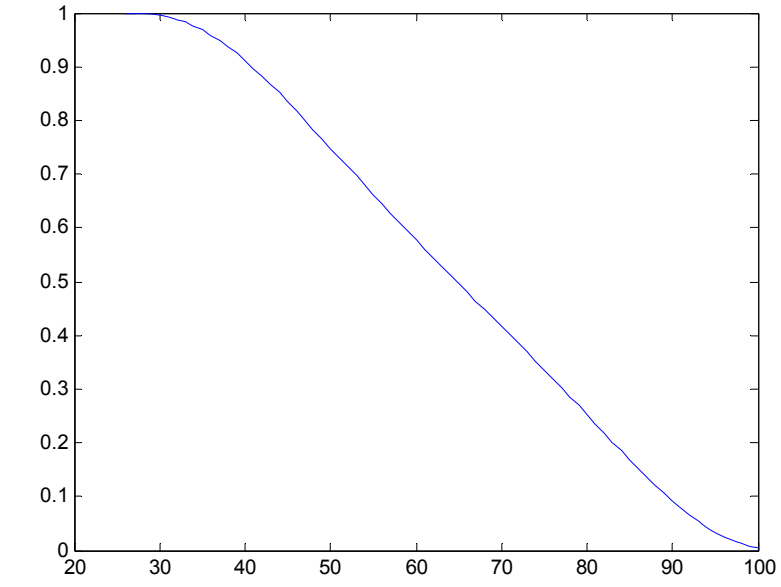

Figure 7: The survival probability of different ages starting at age 25

6. Conclusion

A model of DES is a tool for decision support system. The key feature of any decision model is to be "fit for purpose" for decision-making [25]. A model is a logic mathematical framework that permits the integration of facts and values and that links these data to outcomes for decision makers. If a model built at human disease processes to reasonably inform decision-makers and deal with uncertainty, variability, and heterogeneity, interaction, etc., simulation can appropriately handle the realities to correctly model it at the required depth, although it may involve a large number of computations which may be a hindrance to conducting DES. However, as computing techniques emerge dramatically, DES becomes easy and powerful for various managerial purposes.

Our analysis has two strengths. First, to our knowledge, our study is the first discrete event simulation model of decision analysis to compare competing strategies for chronic HBV infection. Previous models have focus on either the Markov model or decision tree analysis. Second, our model acknowledges the increasing prevalence of simulation models. This approach increases the generalizability of modeling flexibility in light of statistical data.

Our study only demonstrates a possible construction for a DES used in analysis of chronic HBV. Our model has several limitations. First, several of our estimates are based on literature which may depend on different design, patient population, follow-up and quality. Our estimates of patient health preferences may be limited because we adopted utilities for cirrhosis health states in HBV from limited sources. However, it is reasonable to assume that a patient who develops cirrhosis or related complications would have the same quality of life decrement regardless of time. Second, the time period of health states were estimated and adjusted accordingly to systematical consistence of simulation. More conditional health statuses could be included for better results and decision-making processes.

7. Acknowledgements

The authors wish to thank Dr. Y.F. Liaw for valuable comments in treatments for CHB, Mr. Y. Samyshkin in modelling, and IMS Health in supporting Mr. N. Wang and K. Sun in programming for this work.

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Appendix

A Chronic Hepatitis B Virus Infection Model on TreeAge

We use the software TreeAge [24] as a computing tool to compare results of the HBV disease progression with that calculated by the proposed model in this paper. The Markov model in TreeAge [24] is shown as a tree in Figure A. The transitional probabilities between symptoms are defined in the first box of the tree based on Figure 2. For each Markov node, first it will decide that whether or not the patient will die by population mortality or disease progression. If the patient died, then the disease progression will end up with death; if the patient does not die of population mortality, then the patient will make a transfer to another state or simply stay at the previous state. In Figure A, the symbols pDie, pDieDecompensation, and pDieHCC represent the population mortality, the probabilities of death at state decompensation and at state HCC respectively. Besides, pDNA1067_DNA1045 means the transitional probability from state "HBeAg(+) hepatitis HBV-DNA $> 2 \times 10^{6\sim7}$ IU/ml" to "HBeAg(+) hepatitis HBV-DNA$> 2 \times 10^{4\sim5}$ IU/ml". The interpretations for the other transition probabilities are similar. The symbol "#" represents the probability of one subtracting the total probabilities of other transitions above. Note in the first block named "HBV problem", pDie is defined to be that calculated by one subtracting the survival probability in the life table at different ages.

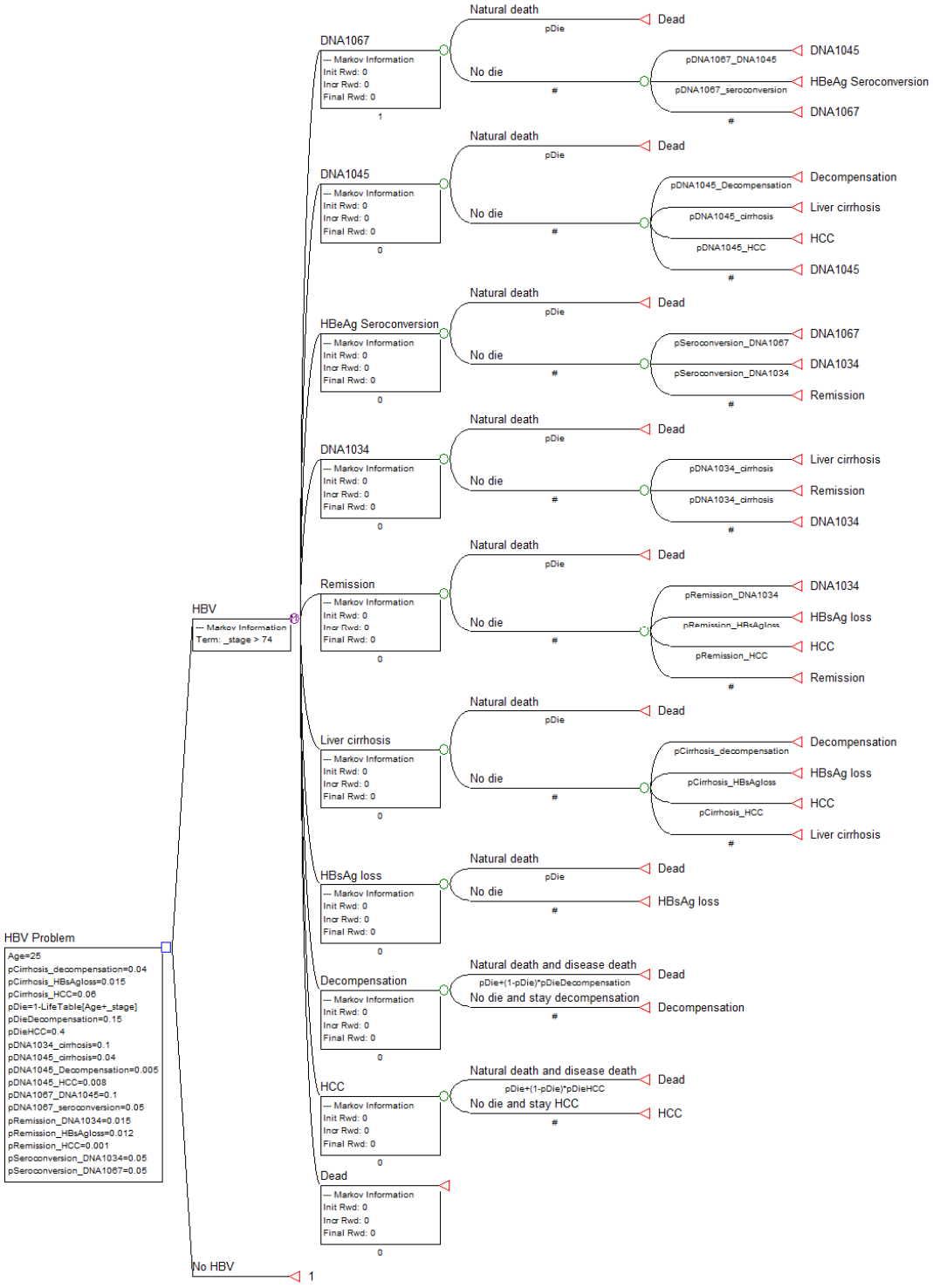


Figure A: The HBV disease progression model in TreeAge.

The survival probability at different ages in Table A is applied to the Markov model with TreeAge as well. Table A shows the simulated disease progression probabilities distribution, which is similar to the result in Table A. The simulated disease progression probability distributions are plotted in Figure B. Moreover, the corresponding survival probability can be computed simultaneously. Figure D shows the

survival curve for the patients infected HBV starting at age 25.

Table A: The simulated disease progression probabilities distribution by using TreeAge

States / Ages	s_1	s_2	s_3	s_4	s_5	s_6	s_7	s_8	s_9	s_{10}
25	1	0	0	0	0	0	0	0	0	0
30	0.4478	0.3274	0.0263	0.0087	0.1378	0.0298	0.0034	0.0047	0.0060	0.0081
35	0.2009	0.3946	0.0118	0.0148	0.2063	0.0795	0.0174	0.0169	0.0162	0.0417
40	0.0899	0.3635	0.0053	0.0170	0.2216	0.1100	0.0371	0.0287	0.0225	0.1046
45	0.0400	0.3024	0.0023	0.0171	0.2142	0.1189	0.0582	0.0358	0.0243	0.1867
50	0.0177	0.2392	0.0010	0.0161	0.1975	0.1130	0.0782	0.0378	0.0232	0.2763
55	0.0078	0.1831	0.0005	0.0146	0.1773	0.0991	0.0953	0.0358	0.0203	0.3662
60	0.0034	0.1363	0.0002	0.0129	0.1554	0.0820	0.1080	0.0314	0.0168	0.4537
65	0.0014	0.0986	0.0001	0.0110	0.1328	0.0646	0.1154	0.0258	0.0132	0.5371
70	0.0006	0.0684	0.0001	0.0091	0.1091	0.0482	0.1155	0.0198	0.0099	0.6197
75	0.0002	0.0447	0.0000	0.0070	0.0844	0.0336	0.1069	0.0140	0.0068	0.7023
80	0.0001	0.0265	0.0000	0.0050	0.0595	0.0212	0.0888	0.0089	0.0043	0.7857

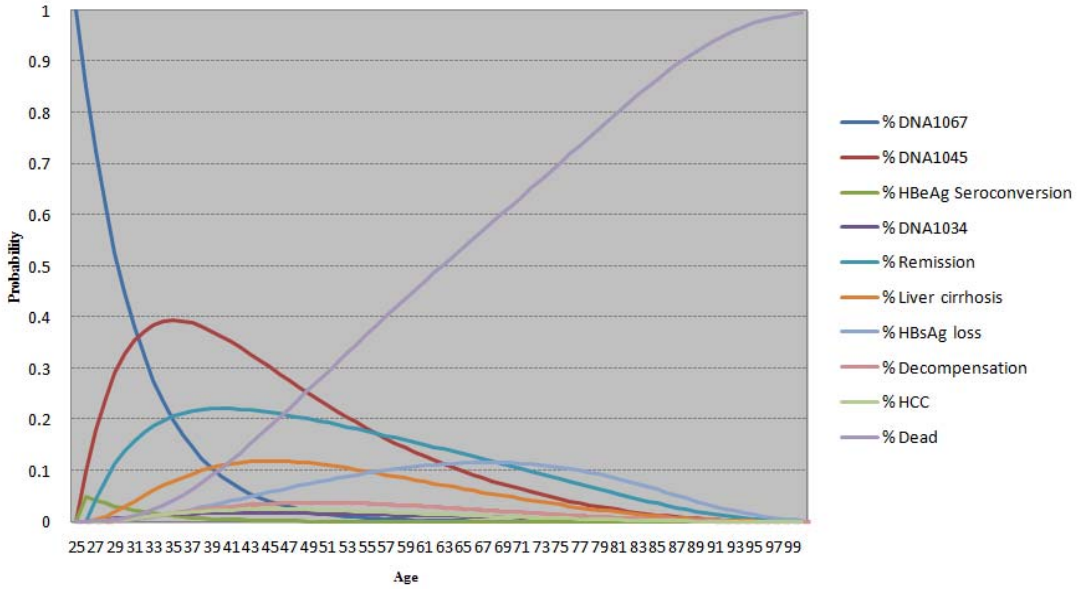


Figure B: Starting from s_1, the simulated disease progression with probabilities at different states by using TreeAge

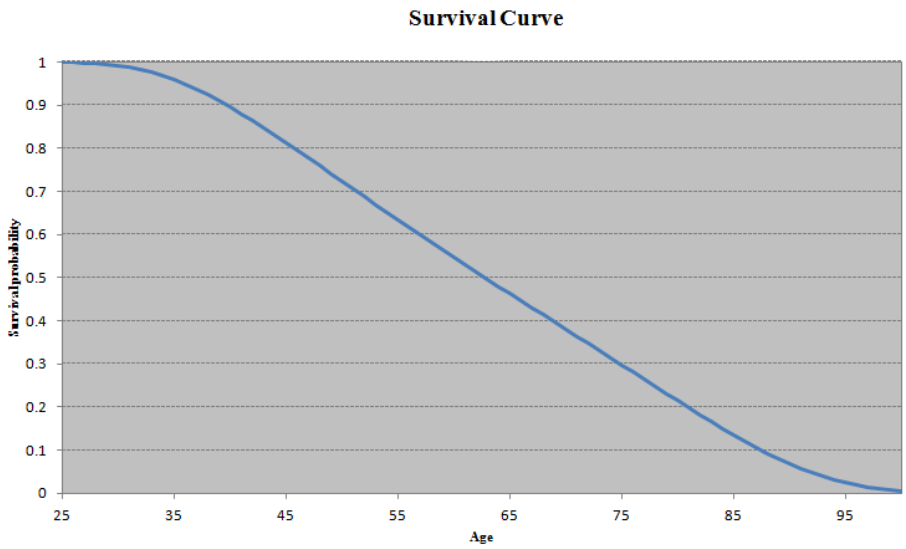


Figure C: The survival curve starting from s_1 computed by using TreeAge

附件五

科技部補助專題研究計畫出席國際學術會議心得報告

日期：__年__月__日

計畫編號	MOST 103-2221-E-004 -003 -		
計畫名稱	離散事件模擬法與慢性肝病進程之預測(Ⅰ)		
出國人員 姓名	陸行	服務機構 及職稱	政大應數系
會議時間	103 年 11 月 9 日 至 103 年 11 月 12 日	會議地點	美國舊金山
會議名稱	(中文) 作業研究和管理科學 2014 年會 (英文) INFORMS Annual Meeting 2014		
發表題目	(中文) 安全檢查系統的等候時間計算研究 (英文) Computing the Waiting Time in a Security Check System		

一、參加會議經過

林蔚君博士是 INFORMS 美國作業研究和管理科學會的國際部的負責人，她希望為臺灣同時也為 INFORMS 努力創造更多的國際聯繫，因此計畫在 INFROMS 的 2014 年會中推銷兩份臺灣主導的國際期刊 Journal of industrial and production engineering (JIPE) 和 International Journal of Operations Research (IJOR)，期待增加更多的學術影響力。於是由張國皓教授、林東盈教授、王逸琳教授和我組織一個場次，特別報告臺灣相關的學術論文。

這是一個超大型的學術會議，據主辦單位估計有將近 5500 人參加這個會議，會議共舉行四天。我們的場次在星期一，參加的人除了對論文主題有興趣的人外，也包括幾位來自歐洲、南美洲、北美洲、亞洲和非洲等國際學術期刊的主要編輯，他們對我們的期刊和論文都給予肯定，也希望 INFORMS 的期刊可以與我們的期刊作更多的互動，給我們很多的建議。

林蔚君博士在會後也邀請國際期刊的編輯和部份 INFORMS 國際部的成員開會討論增加互動的具體作法，希望能為新進人員和博士生製造更多的曝光機會。

因為臺灣已經成立 INFORMS Taiwan chapter，我和王逸琳教授參加 Chapters 的早餐會，我們代表臺灣和其他的成員交換工作經驗，也為國際人士介紹臺灣相關的學術以及學生活動。

二、與會心得

這次報告的論文是 102 年度執行計畫的部份結果，雖然在場的人不都是研究等候模型的，但是也提供許多建議，為未來研究增加議題性和發展性。

三、發表論文全文或摘要

Title: Computing the Waiting Time in a Security Check System

Abstract: The objective of this presentation is to introduce a queueing model to assist the Transportation Security Office understand how to design and manage the security wait environment with customers' satisfaction, for example the normal wait time is no more than 30 minutes. To meet the security conditions in practice, such as checks in various security stages, we use a queueing model with service time of semi-Coxian distributions. The semi-Coxian distribution in fact complicates the computation but reflects relatively better estimation than a traditional model. Thus, it is useful both to maintain the security level and to release the tense in the security check points in airports, or international borders.

四、建議

INFORMS 的學術活動是值得向國人介紹和推廣的。

五、攜回資料名稱及內容

大會議程和 1600 多篇的論文摘要電子檔。

六、其他

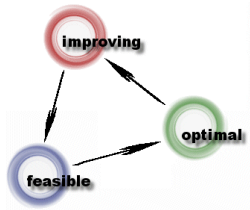
無。

Computing the Waiting Time in A Security Check System

Hsing Luh

Department of Mathematical Science
National Chengchi University
Taipei, Taiwan

INFORMS San Francisco 2014



Outline

Outline

Outline

System State Definition

For constructing a queueing model, consider a two-stage $M/Cox(2)/c_1 \rightarrow /M/c_2/B$ system. First stage has c_1 servers, a buffer of infinite capacity, the second stage has c_2 servers and a buffer of finite capacity of $B - c_2$. First, we define the system state as (n_1, i, j, n_2), where n_1 denotes the number of customers at the first stage, n_2 denotes the number of customers at the second stage, i and j denote the total number of customers in phase 1 and in phase 2 at the first stage, respectively. Then we have the state space

$$\mathbf{S} = \{(n_1, i, j, n_2) |\ i + j = n_1, \text{if } n_1 < c_1;\ i + j = c_1,$$

$$\text{if } n_1 \geq c_1, i,\ j,\ n_1 \in \{0\} \cup \mathbb{N},\ n_2 \in \{0, 1, 2, \ldots, B\}\}.$$

Outline

Outline

Matrix Representation

The infinitesimal generater **Q** is of the block-tridiagonal form and written as follows

$$\mathbf{Q} = \begin{bmatrix} \mathbf{B}_0 & \mathbf{C}_0 & & & & & & \\ \mathbf{A}_1 & \mathbf{B}_1 & \mathbf{C}_1 & & & & & \\ & \ddots & \ddots & \ddots & & & & \\ & & \mathbf{A}_{c_1-1} & \mathbf{B}_{c_1-1} & \mathbf{C}_{c_1-1} & & & \\ & & & \mathbf{A} & \mathbf{B} & \mathbf{C} & & \\ & & & & \ddots & \ddots & \ddots & \end{bmatrix}$$

where the submatrices $\mathbf{A}_{n_1}$, $\mathbf{B}_{n_1}$ and $\mathbf{C}_{n_1}$ are dimensional of $((n_1+1)(B+1) \times (n_1)(B+1))$, $((n_1+1)(B+1) \times (n_1+1)(B+1))$, and $((n_1+1)(B+1) \times (n_1+2)(B+1))$ for $n_1 \leq c_1$ respectively, but $\mathbf{A} = \mathbf{A}_{c_1}$, $\mathbf{B} = \mathbf{B}_{c_1}$ and $\mathbf{C} = \mathbf{C}_{c_1}$ for $n_1 > c_1$.

Submatrices

Define

$$\mathbf{A}_{n_1} = \begin{bmatrix} \bar{\alpha}_0 & \alpha_0 & & & & & \\ \tilde{\alpha}_1 & \bar{\alpha}_1 & \alpha_1 & & & & \\ & & \ddots & \ddots & & & \\ & & \tilde{\alpha}_{C_2-1} & \bar{\alpha}_{C_2-1} & \alpha_{C_2-1} & & \\ & & & \tilde{\alpha}_{C_2} & \bar{\alpha}_{C_2} & \alpha_{C_2} & \\ & & & & & \ddots & \ddots \\ & & & & & \tilde{\alpha}_B & \bar{\alpha}_B \end{bmatrix}$$

where α_k, $\tilde{\alpha}_k$ and $\bar{\alpha}_k$ are the size of $(n_1 + 1) \times n_1$.

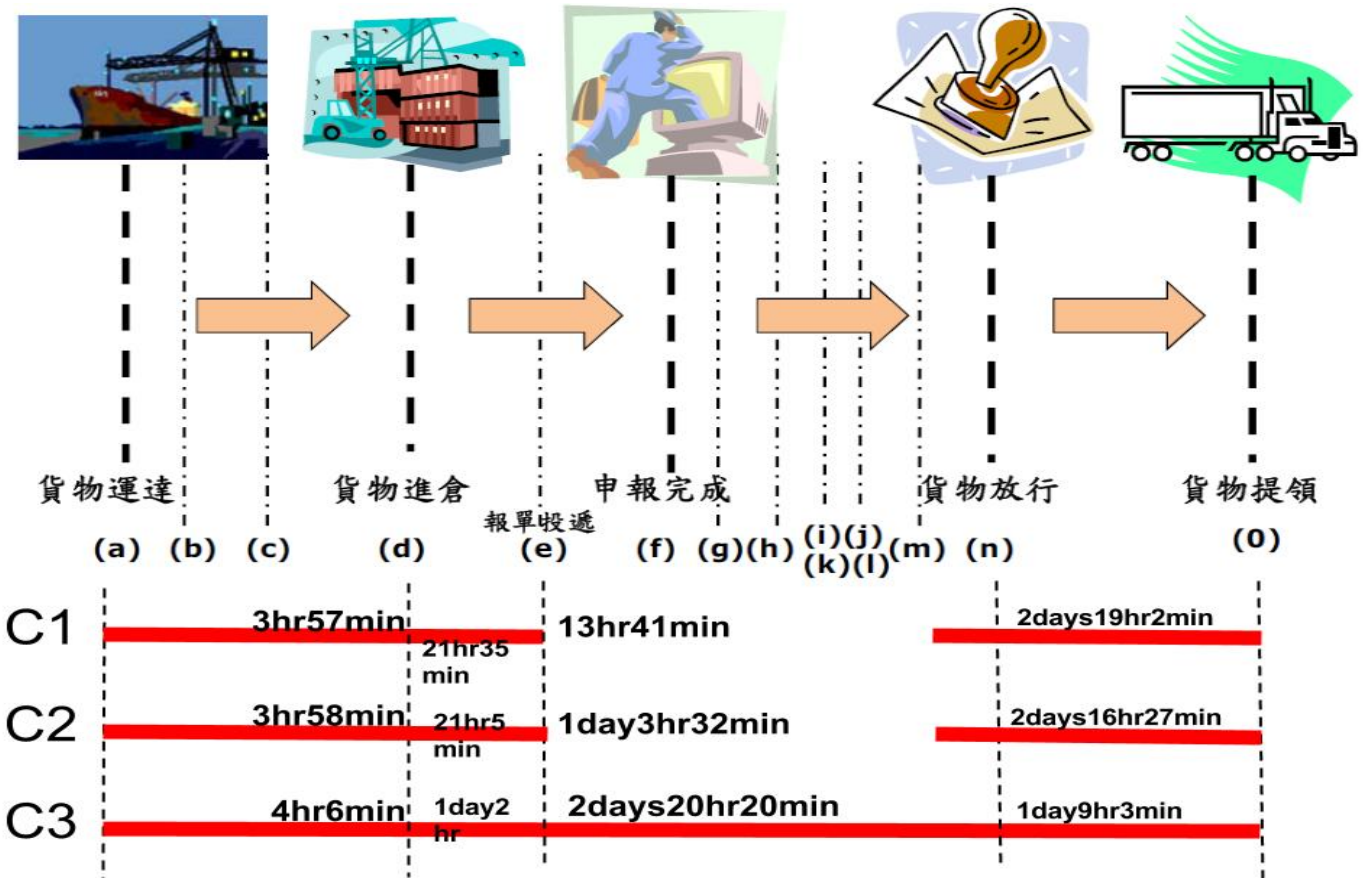
Submatrices

Define

$$\mathbf{B}_{n_1} = \begin{bmatrix} \bar{\beta}_0 & & & & & & \\ \tilde{\beta}_1 & \bar{\beta}_1 & & & & & \\ & \ddots & \ddots & & & & \\ & & \tilde{\beta}_{c_2} & \bar{\beta}_{c_2} & & & \\ & & & \tilde{\beta}_{c_2+1} & \bar{\beta}_{c_2+1} & & \\ & & & & \ddots & \ddots & \\ & & & & & \tilde{\beta}_B & \bar{\beta}_B \end{bmatrix}$$

$\tilde{\beta}_k$ and $\bar{\beta}_k$ are the size of $(n_1 + 1) \times (n_1 + 1)$.

Outline



Stationary state probabilities

Suppose the proportion for the second stage check q_0 and the required mean service time time at the second stage is S_0, which are considered as the security level. Given (q_0, S_0) a security level (q_0, S_0), the minimum arrival rate to the second stage is λq_0 and the minimum mean service time is $S_0 = 1/\nu$. Assume that there are c_2 servers in the second stage. We have an $GI/M/c_2$ model with $A(s)$ as the LST of the arrival process. The stationary distribution of the queue length, denoted by m_j, can be obtained as

$$m_j = Kr_0^j \quad \text{for } j \geq c_2$$

where r_0 is the root of $A[c_2\nu(1-z)] = z$. The constant K and the m_j $(j = 0, 1, ..., B - c_2)$ must be determined from the normalization condition $\sum_{j=0}^{\infty} q_j = 1$ and the the stationary probability balanced equations. A recursive relation for m_j, when $j < c_2$ can be developed as standard results for $GI/M/c_2$ queue.

Suppose that the waiting space for the second stage inspection is limited by size $B - c_2$. Then the tail probability of queue length exceeding N_0 is defined as $\alpha_0 = \sum_{j=N_0+1}^{B-c_2} m_j$. For a given λ, q_0, S_0, there is a minimum requirement $x(\alpha)$ for the system that guarantees the minimum waiting, that is $\lambda q_0 S_0/c_2 < x(\alpha)$ or $c_2 > \lambda q_0 S_0/x(\alpha)$, which gives the range of c_2 for a waiting time with guaranteed percentage. We need to find an appropriate initial c_2 such that a feasible range of $q \geq q_0$ and $S \geq S_0$ with $\alpha < \alpha_0$ exists. This initial feasible staffing level denoted by c_2^0 can be obtained by numerical search over (q, S) subject to the constraint $\alpha < \alpha_0$. Obviously, the larger the c_2^0, the larger the feasible region of (q, S). Note that as c_2 increases, the feasible region of $\alpha < \alpha_0$ will expand. For a given S, we can determine the maximum feasible q_{max}. Thus the feasible q should be in $(q_0, q_{\max})$.

Outline

An optimization Problem

The main issue in a two-stage security-check system is to determine the staffing level for a required security check level and the optimal policy parameter to minimize the average customer waiting time. Let $E(W_i)$ be the expected waiting time in stage i queue, where $i = 1, 2$. For a set of feasible $c_2 > c_2^0$ and $S > S_0$, our problem of finding the optimal (c_1, c_2) can be written as

$$\min_{c_1, c_2} E(W) = (1 - q)E(W_1) + q[E(W_1) + E(W_2)]$$

$$= E(W_1) + qE(W_2).$$

subject to $q_0 < q < q_{\max}$. Suppose the waiting cost rate is h_1 and the staffing cost rate is h_2, a policy (c_1^0, c_2^0, q_0) is said to be dominated, if there exits a policy $(\acute{c}_1, \acute{c}_2, q_0^*)$ so that $h_1\{E(W(q_0)|(c_1^0, c_2^0)) - E(W(q^*)|(\acute{c}_1, \acute{c}_2))\} > h_2\{(\acute{c}_1 + \acute{c}_2) - (c_1^0 + c_2^0)\}$.

Outline

A Search Procedure for Finding the Optimal Feasible q^*

Step 1 : For a given traffic demand and a security check requirement (q_0, S_0), find an initial staffing level c_1, c_2 for the security inspection based on the tail probability constraint of $\alpha < \alpha_0$.

Step 2 : Compute $E(W)$ for $q > q_0$. If for $q > q_1$, $E(W(q)) < E(W(q_1))$, based on the unimodual property of $E(W)$. Thus, q is security-check feasible and can be used as the proportion of customers selected for the second stage inspection with the expected waiting time $E(W(q^*))$. Stop, (c_1, c_2, q) is the policy with optimum. Otherwise, go to the next step.

A Search Procedure for Finding the Optimal Feasible q^*

Step 1 : For a given traffic demand and a security check requirement (q_0, S_0), find an initial staffing level c_1, c_2 for the security inspection based on the tail probability constraint of $\alpha < \alpha_0$.

Step 2 : Compute $E(W)$ for $q > q_0$. If for $q > q_1$, $E(W(q)) < E(W(q_1))$, based on the unimodual property of $E(W)$. Thus, q is security-check feasible and can be used as the proportion of customers selected for the second stage inspection with the expected waiting time $E(W(q^*))$. Stop, (c_1, c_2, q) is the policy with optimum. Otherwise, go to the next step.

Step 3 : If $q < q_0$, any increase in q will increase $E(W(q))$. This is a case where an increased staffing level with a feasible q for the second stage inspection should be considered. For an increased pair $(\acute{c}_1, \acute{c}_2) > (c_1^0, c_2^0)$ such that q^*, q_0, $E(W(q))$ curve will shift so that the optimal q^* may become feasible. To indicate the dependence on (c_1, c_2), we denote the expected waiting time by $E(W(q)|(c_1, c_2))$.

Critical point property

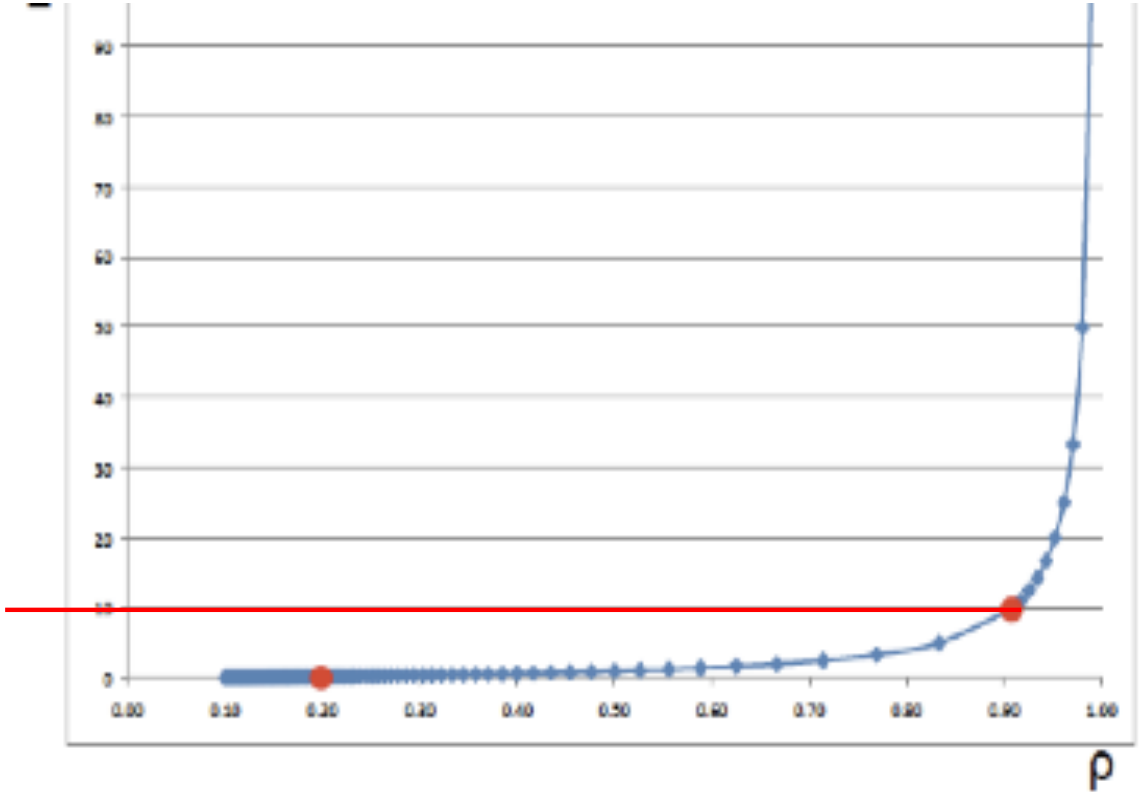


Figure: An average waiting time distribution

科技部補助計畫衍生研發成果推廣資料表

日期:2015/10/06

科技部補助計畫	計畫名稱: 離散事件模擬法與慢性肝病進程之預測(I)
	計畫主持人: 陸行
	計畫編號: 103-2221-E-004-003- 學門領域: 作業研究

無研發成果推廣資料

103年度專題研究計畫研究成果彙整表

計畫主持人：陸行	**計畫編號：**103-2221-E-004-003-
計畫名稱：離散事件模擬法與慢性肝病進程之預測(I)	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數（含實際已達成數）	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
國外	論文著作	期刊論文	1	1	30%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（外國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		

其他成果（無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。）	國際合作和訪問的對象是 Dr. Kenneth Lee and Dr. David Wu。他們協助我開發模擬計算模式和比較模擬結果。因為他們對於亞洲人與馬來西亞人在使用藥物和經濟成本效益之特質和分析的經驗，以及比較了解相關文獻與資料。由此，我可以將離散事件模擬法的計算結果與其比較和調整模式，使其更符合實際的意義。

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

科技部補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估
   ■達成目標
   □未達成目標（請說明，以100字為限）
   　□實驗失敗
   　□因故實驗中斷
   　□其他原因
   說明：

2. 研究成果在學術期刊發表或申請專利等情形：
   論文：□已發表 ■未發表之文稿 □撰寫中 □無
   專利：□已獲得 □申請中 ■無
   技轉：□已技轉 □洽談中 ■無
   其他：（以100字為限）

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）（以500字為限）
   論文的學術成就在於推導 time-nonhomogeneous markov chain 計算的基本性質，以不同的機率條件驗證其收斂性和以不同模式(計算軟體)驗證其可行性。其應用在建立可計算的肝病病程的數學模型和電腦模擬程式。本計畫提供計算肝病病程風險預測的模式，其計算模式可運用相關的研究和支援健保經濟政策擬定。